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ACCINE THERAPY
AND THE
METHOD OF TREATMENT

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VACCINE THERAPY

AND THE

OPSONIC METHOD OF TREATMENT

VACCINE THERAPY

AND

THE OPSONIC METHOD OF TREATMENT

A SHORT COMPENDIUM FOR GENERAL PRACTITIONERS, STUDENTS, AND OTHERS

BY

R. W. ALLEN, M.D., B.S. (LOND.)

LATE PATHOLOGIST TO THE ROYAL EYE HOSPITAL; LATE GULL STUDENT OF PATHOLOGY GUY'S HOSPITAL

SECOND EDITION

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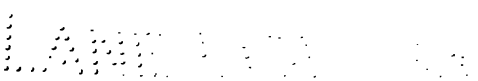

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PREFACE TO THE SECOND EDITION

THE very kind reception accorded to the First Edition, alike by critics and by those for whose use it was designed, has encouraged the production of this Second Edition. My best thanks are due to friends and reviewers who pointed out several defects and slight mistakes; these, I trust, they will find lacking in the present volume. As regards certain views and theories to which exception was taken, adequate reasons for their revisal have not been demonstrated, and they are retained. So great has been the progress of vaccine therapy during the past year that such enlargement has been necessitated as almost to justify the present volume being regarded as a new book. So conclusive has been the evidence adduced of the favourable influence of vaccine therapy, when employed by skilled hands in suitable cases, that no longer is the help of the immunizator being sought only when all other measures have failed; he is now regarded as a useful adjuvant to such other therapeutic aids as clinical experience has proved appropriate; and at no time has the future of vaccine therapy seemed so bright, and its place in practical surgery and medicine so assured, as it does at present. To my friend Mr. F. L. Armitage

57693

my best thanks are due for the use of his very complete list of references to the work done during the past year, and for his help with the manuscript; and, among others, to Drs. Houston, Wynn, Stewart, Benham, Williamson, Captain Forster, I.M.S., and Colonel Semple, I.M.S., for reprints and other useful information.

58B, WIMPOLE STREET, W.
September, 1908.

PREFACE TO THE FIRST EDITION

So prominent a place is this method of treatment now assuming in medical practice, and so scattered is the literature concerning it, that the time seemed ripe for an endeavour to collect such facts as might suffice to give a general idea of the subject. Theories and opinions have been kept within as small bounds as possible, and prominence given to the results achieved in actual practice. No pretence is made of completeness, but it is hoped that the great and ever-increasing utility of opsonic work may have been adequately demonstrated. My best thanks are due to Dr. J. W. Eyre for corrections and suggestions, and for the loan of Charts XI. and XII., and to other friends for revision of certain sections.

Beginners may find it advantageous to defer the reading of Chapter I. until the end.

58B, WIMPOLE STREET, W.
November, 1907.

CONTENTS

INTRODUCTION

HISTORY OF ORIGIN OF VACCINE THERAPY

CHAPTER I

OPSONINS: WHAT THEY ARE, THEIR NATURE AND SOURCE

PAGES

The method of demonstrating the presence of opsonins in blood-serum—The nature and constitution of opsonins—Their superficial resemblance to ferments—Their relationship to other immune bodies—Specific and non-specific opsonins—Anti-opsonins—Site of formation in the body—Their fate in the organism - - - - - - - 4—16

CHAPTER II

PRINCIPLES INVOLVED IN VACCINE THERAPY

Relationship of infection to opsonic power of the blood—Effects of injection of a bacterial vaccine—Negative and positive phases—Regulation of dosage—Other methods of raising the index—Other considerations besides elevation of index 17—28

CHAPTER III

DETERMINATION OF THE OPSONIC INDEX

Definition of the opsonic index—Method of its determination—Its accuracy discussed—Other methods of estimating the opsonic content of the blood - - - - 29—44

CHAPTER IV

PREPARATION OF THE VACCINE

PAGES

Preparation of the bacterial vaccine—Isolation and cultivation of the various organisms—Preparation of the emulsion; its standardization, sterilization and tubing—The various forms of tuberculin—Preparation of combined vaccines—Method of administration - - - - - - - 45—70

CHAPTER V

THE OPSONIC INDEX IN HEALTH AND DISEASE: ITS VALUE IN DIAGNOSIS, PROGNOSIS, AND TREATMENT

The normal variations of index—Effects of exercise, food, and starvation—The index in infancy—The index in disease—Effect of exercise—Auto-inoculation—Effect of menstruation—The index as an aid to diagnosis in tuberculosis and other infections—Special methods of employing it—As an aid to prognosis—Its value as a guide in the therapeutic production of immunity - - - - - - - 71—95

CHAPTER VI

INFECTIONS BY THE TUBERCLE BACILLUS

Ætiology of tuberculosis—Methods of establishing a diagnosis of tubercular infection—Necessity for determination of variety of bacillus at work—Human and bovine types—Methods of differentiating the two—Varieties of tuberculin: their properties and actions—Conduct of case (*a*) by opsonic methods; (*b*) by clinical signs—Apyrexial and pyrexial cases—Mixed infections—Results obtained by use of tuberculin in phthisis—Comparative statistics—Results obtained in other tuberculous infections - - - - - - 96—149

CHAPTER VII

THE STAPHYLOCOCCUS

Acne—Boils and carbuncles—Sycosis—Periostitis and osteomyelitis—Septicæmia and pyæmia—Cases—Dosage and time for administration - - - - - - 150—156

CHAPTER VIII

THE STREPTOCOCCUS

PAGES

The streptococcus a large genus—Varieties—Ulcerative endocarditis—Septicæmia and pyæmia—Erysipelas—Rheumatism and chorea—Scarlet fever and other infections - 157—166

CHAPTER IX

THE PNEUMOCOCCUS

The index in pneumonia—Vaccine therapy in acute pneumonia—Unresolved pneumonia—Empyema—Peritonitis - 167—171

CHAPTER X

THE GONOCOCCUS

The opsonic index in gonococcal infections, and its utility in diagnosis and treatment, with cases and charts—Urethritis, acute and chronic arthritis, vulvo-vaginitis - - 172—183

CHAPTER XI

THE VACCINE THERAPY OF CATARRH, NASAL AND TRACHEAL, AND OF THE ACCESSORY AIR SINUSES

The bacteriology of catarrh—Vaccine therapy of catarrh, with illustrative cases - - - - - 184—191

CHAPTER XII

THE COLON, TYPHOID, AND DYSENTERY GROUPS

THE COLON GROUP: Illustrative cases—Cholecystitis—Appendicitis—Endometritis—Puerperal fever—Cystitis, etc. - 192—196

THE TYPHOID GROUP: *Bacillus typhosus* — The paratyphoid bacilli—Types of fever—Methods of diagnosis—Isolation of bacteria from blood—Widal's test—Anti-typhoid immunization—Preparation of anti-typhoid vaccine—Effects of inoculation—Typhoid carriers—Treatment of enteric fever with sera and vaccines - - - - - 196—202

THE DYSENTERY GROUP: Clinical types of bacillary dysentery—Their vaccine therapy—Dosage and results - - 202—205

CHAPTER XIII

THE *MICROCOCCUS MELITENSIS*, *BACILLUS PARALYTICANS*, *MICROCOCCUS NEOFORMANS*, MENINGOCOCCUS, ACTINOMYCOSIS - - - 206—214

CHAPTER XIV

VACCINE THERAPY IN EYE DISEASES

Tuberculous keratitis, iritis, choroiditis—Conjunctivitis due to tubercle bacillus, pneumococcus, gonococcus, bacillus of Friedländer, bacillus of Morax-Axenfeld—Corneal ulcers —'Hordeolum'—Meibomians—Dacryocystitis - 215—226

APPENDIX

Opsonic index determinations—Special points of importance in respect to certain bacteria—The tubercle bacillus—Special methods for its detection in sputum, fæces, and urine—Cultural methods—Special staining methods for human and bovine varieties —'Splitter'— Effect on the index to the human strain of injections of T.R. of bovine origin —The Index to both types in certain cases of pulmonary phthisis, with charts - - - - - - 227—235

INDEX - - - - - - - - 236—244

VACCINE THERAPY

AND THE

OPSONIC METHOD OF TREATMENT

INTRODUCTION

It was in 1798 that Jenner gave to the world the results of his observations and experiments upon small-pox and the production of an artificial immunity against it, under the title 'An Inquiry into the Causes and Effects of the Variola Vaccinæ.'

Although we are as yet ignorant of the cause of small-pox, and can only conjecture upon the nature of vaccination, we have, from analogy with other similar processes, reason for the belief that it consists of an active immunization by the agency of an attenuated form of the causal organism.

In Jennerian vaccination we find the genesis of the opsonic form of treatment, and although the two processes are really very different in nature, the connection is preserved in the name 'vaccine,' somewhat indiscreetly given to the killed bacterial emulsions now employed. The name is certainly an ill-chosen one, inasmuch as the laity at once think of all the arguments of the conscientious objector, and hesitate about submitting themselves to what they firmly believe to be a process identical with vaccination.

Pasteur carried on the work initiated by Jenner, and endeavoured in divers directions to induce a prophylaxis by the inoculation, mostly in an attenuated form, of the bacterial agents themselves or products derived from them.

Koch, in 1890, however, was the first to attempt the cure of an infection by a specific remedy—viz., of tuberculosis by means of tuberculin. Unfortunately, doses far in excess of those now employed were used, with the result that tuberculin fell into grave disrepute.

Denys and Leclef immunized rabbits against streptococci, and showed that the resultant increased phagocytosis was due not to any changes in the leucocytes, but to an alteration in the serum; they demonstrated that the leucocytes of the immunized animal, when placed in normal serum, showed no greater phagocytic activity than did normal leucocytes.

The studies of Leishman on phagocytosis paved the way for the discoveries of Wright upon the bactericidal agents present in the blood, and in especial of the one to which he gave the name of 'opsonin.' Having devised a means of accurately estimating the opsonic content of the blood, he was thereby enabled to learn the reason of the previous failures of tuberculin, more or less to obviate the attendant danger, and place the opsonic method of treatment of tuberculosis upon a scientific basis.

Pfeiffer claims priority to Wright for the discovery of the production of immunity by the injection of killed bacterial cultures, while Neufeld and Rimpau (1904), independently of Wright, discovered that the substances in antistreptococcal and antipneumococcal sera favouring phagocytosis united with the bacteria and were thermostable. To Wright, however, is due the entire credit

of originating the idea of estimating the changes in the opsonic content of the blood as guidance in the therapeutic use of bacterial vaccines. The seed he sowed has flourished greatly—how greatly the following pages will briefly indicate—and it would appear that to the genesis of a new, of a scientific, system of medicine the impulse has now been given. The medicine of the future is the medicine of vaccines and of sera. The empiricism of the past will give way to methods based upon scientific knowledge, and the public will no longer look upon medicine with a sceptical eye, and dose themselves with ineffective nostrums. The surgeon will triumph where now he fails, and, armed with additional power, he will not fear the inroads of bacterial invasion.

CHAPTER I

OPSONINS: WHAT THEY ARE, THEIR NATURE AND SOURCE

Of the means whereby the body tissues are enabled to overcome bacterial invasion our knowledge is as yet far from perfect. The process is admittedly a very complex one. Various substances, to which the names 'agglutinins,' 'precipitins,' 'stimulins,' 'lysins,' and 'opsonins,' are given, are considered each to play a part in enabling the phagocytic cells to complete the destruction of the infecting bacteria. Metchnikoff holds that the principal part is played by the substances to which he has given the name 'stimulins.' The presence of these in the tissue fluids he has not yet succeeded in satisfactorily demonstrating, but considers their function to be that of acting upon the phagocytes so as to stimulate them to perform phagocytosis. While not denying the existence of opsonins, he assigns to them but a secondary part. Wright, on the other hand, has demonstrated beyond doubt the presence in the blood of substances which act upon the bacteria, and get them ready for the completion of their destruction by the phagocytes. To these bodies he has given the name of 'opsonins.' It would appear possible for phagocytosis to proceed without prior opsonization of the bacteria, unless it be argued —and this seems very plausible—that the phagocytic cells contain opsonins in their plasma fluid from which it is

hardly possible to free them. Be this as it may, it is beyond question that the presence of opsonin materially assists the processes of phagocytosis.

The method whereby the presence of opsonin in blood-serum is demonstrated is as follows: A little freshly-drawn blood is immediately received into eight or ten times its volume of 2 per cent. sodium citrate to prevent coagulation. The blood-cells are then thrown down by rapidly centrifuging, and the supernatant liquid pipetted off. The cells are then thoroughly washed with a considerable bulk of a solution of 0·8 per cent. sodium chloride in distilled water, and again thrown down by means of the centrifuge, this process being repeated two or three times, so that finally the cells are washed practically free from all blood-plasma, and are left suspended in a very small volume of the normal saline solution, as uniform a mixture as possible being made. A twelve to eighteen hour old culture on agar of any organism—say *Staphylococcus albus*—is then taken, and a thick emulsion made with a solution of 0·1 per cent. sodium chloride in distilled water. Clumps are thrown down by means of the centrifuge, and the bacterial emulsion divided into two parts, *A* and *B*. *A* is set aside; to *B* an equal volume of fresh blood-serum is added, and the two thoroughly mixed together and heated in an incubator at 37° C. for fifteen minutes. The bacteria are then thrown down by means of the centrifuge, and as much liquid as possible pipetted off. The bacteria are well washed with 0·1 per cent. solution of sodium chloride in distilled water, and again thrown down, this process being repeated several times. Finally, an emulsion of the bacteria is made in the salt solution exactly like *A*, and the numbers present respectively in emulsions *A* and *B* counted, the thicker emulsion being then diluted to exactly the same strength as the weaker. We have

then a suspension of blood-cells of which unit volumes contain the same number of polymorphonuclear white cells—*i.e.*, of phagocytes—and two emulsions of the same strength of a given organism in 0·1 per cent. salt solution, differing only in the fact that the bacteria in one (*B*) have been acted upon by blood-serum at 37° C. for fifteen minutes. If this has had no action upon the organisms, then identical results should be obtained by the following procedure: Equal volumes of the blood-cells and the bacterial emulsion *A* are then thoroughly mixed together in a capillary pipette and incubated at 37° C. for fifteen minutes, the same being done with the substitution of emulsion *B* for *A*. Films are then spread, stained by Leishman's method, and observed under a $\frac{1}{12}$-inch oil-immersion lens. The number of bacteria engorged by 100 polymorphonuclear leucocytes is then counted upon each film. An experiment performed in this way gave the following result:

Bacterial Emulsion employed.	Number of Cocci in 100 Polymorphonuclear Leucocytes.
A	10
B	500

It is thus obvious that some change is produced in the bacteria by the action of the blood-serum whereby phagocytosis is expedited. To the substance by which this change is brought about Wright gave the name 'opsonin.'

The Nature and Constitution of Opsonins.

Until they have been isolated and obtained in a state of purity it is obvious that the exact constitution of opsonins cannot be determined.

Certain observations render the view probable that they are of a proteid nature. Thus, Yorke[1] filtered normal

[1] *Biochemical Journal*, vol. ii., June, 1907, p. 357.

serum through a sterile Chamberland candle under very high pressure, and found that the opsonin passed readily through for the first few minutes, but that after that only traces permeated the candle-wall, owing to the pores being filled up by the proteids of the serum. The residue in the filter, beside containing comparatively unaltered serum consisted also of a gelatinous substance, adherent to the sides of the candle and of high opsonic power. It would thus appear that opsonins will not pass through a Chamberland candle the pores of which have been blocked up with gelatine or proteid substance. They would therefore appear to be of a 'colloidal' nature. Lamar and Bispham[1] showed also that they were not dialysable, and that they are carried down with the euglobin when serum is half saturated with ammonium sulphate.

In certain respects they bear some resemblance to the ferments. Thus, serum can be diluted to a considerable extent without marked lessening of its opsonic power. Noguchi[2] has also shown that they are not destroyed by drying the serum at 23° C., and that in this desiccated state they retain their activity after two years, and are, moreover, comparatively resistant to heat. Exposure to a temperature of 120° C. but slightly impairs their power, which is not altogether destroyed by a temperature of 150° C.

Like ferments, opsonins are also very sensitive to slight alterations in the acidity or alkalinity of the medium in which they are dissolved, displaying the greatest activity in a solution of neutral reaction. As regards their biological constitution diverse views are held. It would, however, appear that the opsonins present in normal serum and in that of an infected or immunized animal, which is known as an 'immune' serum, are not quite the

[1] *Journal of Experimental Medicine*, December, 1906.

[2] *Ibid.*, vol. ix., No. 4, p. 455.

same thing, and the elucidation of this question has been much hindered by the failure, especially of the earlier investigators, to recognize this possibility.

The following experiment of Yorke and Smith[1] upon normal serum corrected earlier observations by Bulloch and Western, and has been amply confirmed by other investigators. A strong emulsion was made of anthrax bacilli in 0·9 per cent. NaCl solution, and killed by heating at 100° C. for thirty minutes. The bacilli were then thrown down by centrifuge, and washed thrice with 0·9 per cent. NaCl solution. The washed dead bacteria were then made up into a strong emulsion, and added to two equal portions of ' normal ' serum, *A* and *B*. *A* was incubated at 37° C. for thirty minutes, *B* for sixty minutes.

The bacteria were then thrown down, and the supernatant sera tested for opsonin with staphylococcus and anthrax. The control sera were diluted to an equal extent with 0·9 per cent. NaCl solution and incubated for similar times with the like organismal emulsions. The figures obtained from the films prepared were as follows :

TABLE I.

	Number of Bacteria phagocytosed by 50 Leucocytes.	Index.
A.—I. ANTHRAX :		
Control serum	40	1·00
Treated serum	8	0·20
II. STAPHYLOCOCCUS :		
Control serum	341	1·00
Treated serum	87	0·25
B.—I. ANTHRAX :		
Control serum	48	1·00
Treated serum	2	0·04
II. STAPHYLOCOCCUS :		
Control serum	395	1·00
Treated serum	70	0·17

[1] *Biochemical Journal*, vol. ii., December 19, 1906.

Other experiments gave similar results, which have been confirmed by Simon, Potter, and others. It therefore appears that the incubation of a large number of any organism with serum will not only greatly reduce the contained opsonin for that given bacterium, but those for other organisms as well. In other words, much the greater proportion of the opsonin present in 'normal' serum is 'non-specific.' As to how much of the remaining proportion of the opsonin is 'specific,' exact observations are lacking.

Numerous experiments have been performed which demonstrate a difference in the behaviour of the opsonins of 'normal' and 'immune' sera. Thus, Bulloch and Western repeatedly tested the serum of human beings against both staphylococcus and the tubercle bacillus. Injections of tuberculin were then given, and found to produce a rise in the tuberculo-opsonin, while not affecting the staphylococcic opsonin. Injections of killed staphylococci had the reverse effect.

The fact, too, that infected patients are found to have either a high or a low index towards that particular organism, and a normal index towards all others, points to an alteration in the opsonin produced by the infection. That this has resulted in the production of a 'specific' opsonin is rendered probable by numerous observations, of which the following may be given as an example:

If two sera, *A* and *B*, be taken, *A* being a 'normal' serum, *B* that of a person infected by the tubercle bacillus —*i.e.*, an 'immune serum'—and each of these sera be divided into two portions, the one of which is heated at 60° C. for half an hour, the other not, and the opsonizing power of these four specimens of serum towards the

tubercle bacillus be estimated, a result like that set out in the following table will be obtained :

	Normal Serum.		Immune Serum.	
	Unheated Portion.	Heated Portion.	Unheated Portion.	Heated Portion.
Bacteria in 100 leucocytes	300	15	200	80

Whereby it is seen that the effect of heating the serum has been very different in the cases of the 'normal' and 'immune' sera respectively. In other words, the amount of 'thermostable' opsonin for the tubercle bacillus is much greater in the 'immune' than in the 'normal' serum.

A comparison of the opsonizing powers towards staphylococcus in the case of these sera would reveal no difference in behaviour.

It is therefore probable that, as a result of the tubercular infection, the amount of 'specific' thermostable opsonin has been increased.

To sum up, while it must be admitted that the demonstration of 'specificity' of opsonins even in 'immune' sera is not complete, it is yet highly probable that in the blood-serum of a perfectly healthy individual there is a minimal amount of opsonin specific against the various pathogenic bacteria, while much the greater proportion is non-specific. The suggestion has been made that opsonin does not so exist in blood or tissue plasma as such, but as 'opsinogen,' needing contact with bacteria or other substances for the formation of 'opsonin,' just as 'fibrin' exists in the blood as fibrinogen, needing calcium salts for its conversion into fibrin. In an individual infected by a given bacterium the amount of opsonin

specific against that bacterium undergoes considerable variation from the normal, and is probably increased in every case, not necessarily beyond the amount of 'specific' opsonin which the healthy individual is capable of elaborating, but beyond the amount which he actually does normally elaborate. Assuming that among the other protective mechanisms of the body a quantity '*A*' of 'specific' opsonin is necessary to enable a given individual to overcome an infection by a certain bacterium, his capacity for elaborating this specific opsonin '*A*' may be in excess, exactly adequate, or in default. In the first and second instance the infection will be overcome in a time varying, *inter alia*, with the amount of specific opsonin elaborated. In the last instance it will not be overcome until such time as his capacity is raised to the necessary point, or unless the other defensive mechanisms of the body suffice.

As regards the structure of opsonins, the following possible views all have their advocates—

1. That opsonins are identical with certain other immune bodies.

(1) Ambocepters (Savtchenko).

(2) Complements (Levaditi, Inmann).

2. That opsonins are not identical with these other bodies, but—

(1) Have a simple structure like toxins, agglutinins, precipitins, amboceptors, complements; or—

(2) Have a double structure, like cytotoxins and hæmolysins, needing the co-operation of a thermostable, amboceptor-like body, and a thermolabile complement-like body (Muir and Martin, Dean, Cowie, and Chapin, etc.).

3. That opsonins are unlike any other antibody, and form a class by themselves (as originally upheld by Wright

and Douglas, Bulloch and Atkin, Keith, Hektoen, Neufeld, and others).

To enter into a full discussion of all these possibilities is quite outside the scope of this book; the theory rendered most probable by the weight of present evidence is the second of these, which may be enunciated as follows: Opsonic action is the effect of two bodies acting together —one, thermostable and of amboceptor-like nature, is the essential substance; alone, it is perhaps capable of opsonizing, but its activity is greatly increased by the presence of a thermolabile, complement-like body. The amboceptor-like constituent is present only in very small quantity in normal serum; hence the apparent thermolability of the opsonin in normal serum, whereas in an 'immune' serum the amboceptor plays the predominant part; and though heating results in a loss of activity, this is only partial. In the case of both normal and immune serum this loss is due to the destruction of the complement-like constituent. Considerable support is lent to this view by recent experiments, and notably those of Cowie and Chapin,[1] whereby they showed—

1. That heated normal serum may be reactivated by the addition of small amounts of fresh normal serum, a phagocytosis resulting which is greater than the sum of the phagocytoses of the sera taken separately. A similar result is obtained with heated 'immune' serum—*i.e.*, the addition of complement in the fresh serum assists the amboceptors of the heated serum.

2. That just as ordinary amboceptors can effect combinations at the freezing-point, while complements cannot, so with opsonins. Thus, normal serum may have its

[1] *Journal of Medical Research*, October, 1907, and February, 1908, p. 57 and p. 95.

opsonic power for staphylococcus removed by addition of sufficient staphylococci, the mixture being maintained at a temperature near 0° C. throughout.

That this has resulted in the binding of the amboceptor-like constituent while the complement remains free is shown by the fact that serum so treated—the bacteria with bound amboceptor having been removed by centrifuge—may still have the power to reactivate a heated serum.

3. Bacteria so treated—*i.e.*, bound to amboceptor—if thoroughly washed with cold salt solution to remove adherent complement, are not much more susceptible to phagocytosis by blood-cells, washed free from complement, than they were before; but the addition to the mixture of complement, either in a little dilute normal serum or in serum inactivated by contact with bacteria in the cold, results in a phagocytosis greatly above the normal.

4. Staphylococci so treated—*i.e.*, bound with amboceptor—are much more easily opsonized by dilute normal serum, or by serum which has been inactivated by contact with staphylococci in the cold, than are the same bacteria not so treated.

5. That a heated serum loses its power to be reactivated if previously treated with a sufficient number of staphylococci—*i.e.*, if it has its amboceptors thus removed.

Further support is lent to this view by the fact, pointed out by Muir and Martin (1906 and 1907), that in the case of the thermolabile constituent of normal serum various substances which absorb complement also absorb opsonin—viz., erythrocytes, bacilli, and serum—when combined with their corresponding antibodies—viz., hæmolytic and bacteriolytic amboceptors and precipitins respectively—whereas these substances have little or no effect upon the thermostable constituent of an immune serum.

ANTI-OPSONINS : SPECIFIC AND NON-SPECIFIC.

Hektoen and Ruediger[1] have shown that many substances, such as calcium and barium chlorides, sodium bicarbonate, lactic acid, and alcohol have the power of inducing a marked general fall in the opsonic power of the blood-serum. The addition of any alkali has the same effect as has that of any acid after the alkaline reaction of the serum has been reduced past the point of neutrality. These substances would therefore appear to be non-specific anti-opsonins. Upon the other hand, if a healthy man be injected with antitetanic serum, a specific rise in the tetano-opsonic index first occurs. This is followed, however, by a general fall. Thus, the staphylococcal, tuberculo-, and tetano-opsonic indices all fall below normal (Yorke and Smith[2]). A similar, though less marked, general depression is observed after injection of antistreptococcal or antidiphtheritic serum. R. Bradshaw[3] has recorded the following observations upon the effect of injections of antidiphtheritic serum upon the tuberculo-opsonic index.

TABLE II.

No. of Case.	Interval since Antidiphtheritic Serum given.	Index.
1	2 days	1·30
1	5 ,,	0·64
2	12 ,,	1·02
2	25 ,,	0·35
3	27 ,,	0·89
3	41 ,,	0·72
4	25 ,,	0·64
5	26 ,,	0·72
6	26 ,,	0·62
7	27 ,,	0·77
8	28 ,,	0·69
9	3 months	0·47

[1] *Journal of American Medical Association*, May, 1906.
[2] *Biochemical Journal*, 1906, p. 341.
[3] *Lancet*, May 19, 1906, p. 1387.

Other observers do not, however, altogether agree with these observations of Bradshaw, but find that the initial fall does not usually last nearly so long as is indicated above, and is followed by a pronounced subsequent rise. So much is this the case that marked improvement is claimed to have been observed in tubercular subjects to whom antidiphtheritic serum has been administered.

The experiments of Hektoen and Ruediger (*supra*) confirm the conclusion that the injection of these sera results in the formation of specific anti-opsonins.

Site of Formation of Opsonins.

That opsonin is not formed in the blood is practically certain. The amount of opsonin present in the blood bears no definite relation soever to leucocytosis, nor is it affected by disease of the blood-forming organs. Evidence is forthcoming that it is a product of muscular or subcutaneous activity. Allen has shown both in man and animals that if limbs be thoroughly perfused with normal salt solution to remove all blood, and the muscles cooled and minced and their plasma extracted in the usual manner, that the index of this plasma, despite slight dilution with the saline solution used in the perfusion, is markedly higher than that of the blood-serum towards various organisms. In the instance of an amputated leg the index of the muscle-plasma compared with that of the patient's serum was 1·4 towards the bacillus of Friedlander, the tubercle bacillus, and *Staphylococcus aureus*. In another case it was found to be 1·3.

The only possible conclusion is that actual formation of opsonin occurs in the muscle tissues, and passes thence into the blood. This explains the experience of Wright[1]

[1] *Lancet*, August 24, 1907, p. 494.

that a certain case of tubercular ulceration which had previously defied treatment did well when the tuberculin was injected in a concentric manner around the area of ulceration.

Fate of Opsonins in the Organism.

As regards this question but little is known. It, however, appears that all exudates and secretions contain certain amounts of opsonin. Lawson[1] finds that it is contained in appreciable amount in the sweat, and to a larger degree in the urine, and that this excreted opsonin is increased during a negative phase consequent upon the injection of a bacterial vaccine. Milk also contains opsonin, perhaps to the extent of a quarter or a fifth of that of the blood, so that the question as to whether the opsonin of the mother's milk can be absorbed through the alimentary tract of the infant attains considerable importance. Wells,[2] from a study of the indices of breast-fed and artificially-fed infants, has concluded that no advantages in this respect are possessed by the former over the latter.

[1] *Lancet*, September 7, 1907, p. 704.
[2] *Practitioner*, May, 1908, p. 635.

CHAPTER II

PRINCIPLES INVOLVED IN VACCINE THERAPY

The Relationship of Infection to the Opsonic Index.

Whether fall of index be antecedent to, or the result of, infection it is as yet impossible to say, but the following observation clearly shows that infection and lowered opsonic content of the blood go hand in hand. A case of chronic cold due to Friedländer's bacillus that had been injected some time previously with the corresponding vaccine had an index of 2·6. Twelve hours later an acute attack began to come on with sneezing and shivery feeling. A specimen of blood was taken, and the index found to have fallen to 2·0. Prompt treatment was adopted and an injection of vaccine given, which stopped further progress of the oncoming cold.

That the fall of index is antecedent to, and not the result of, infection is rendered highly probable by the recent demonstration, referred to later, of the existence of specific and non-specific anti-opsonins, often of a simple chemical constitution, and by the following consideration: Many people, otherwise perfectly free from acne, frequently develop a crop of pustules when suffering from constipation. Their resistance—*i.e.*, their opsonic index to staphylococcus—is usually normal, but may be assumed to be so lowered by the absorption of toxins—

i.e., of anti-opsonins—from the bowel that infection then occurs. Infection having occurred, their index may remain low, in which event the acne will become chronic, or rise to, or over, normal, in which case recovery soon ensues.

Per contra, the throwing off of an infection is accompanied by rise of index. An old sufferer from chronic colds, who had been injected a month previously, had an index to Friedländer's bacillus of 1·5. All the symptoms of a fresh cold appeared, but, as the patient said, he felt he had the cold beaten from the start, and little wonder, for in twenty-four hours the index rose to 5·8, and the patient was perfectly well.

Effect upon the Opsonic Index of Injection of a Bacterial Vaccine.

The statement is usually made that the result of the injection of a bacterial vaccine upon the index to that organism of a healthy person is very slight. Any subsequent depression of the index is stated to be of a very temporary character and of only small extent, while the rise of index which follows the return to the normal is also of a limited and slight character. This statement is substantially true for the tubercle bacillus, but does not hold equally for other organisms, as the following experiments will show :

Experiment I.—An injection of 250,000,000 dead organisms of the *Bacillus septus* was given to a healthy person not infected by that organism, and samples of blood taken on injection and after intervals of three, six, twelve, eighteen, twenty-four, thirty-six, forty-eight, seventy-two, and ninety-six hours. The comparative

opsonizing powers of the various sera towards the *Bacillus septus* were then determined in the usual manner, with the following results :

TABLE III.

Serum	1	on injection			882	bacilli	in 200	cells.	Index = 1·00
,,	2	after 3	hours		544	,,	,,	,,	0·62
,,	3	,, 6	,,		885	,,	,,	,,	1·00
,,	4	,, 12	,,		804	,,	,,	,,	0·91
,,	5	,, 18	,,		949	,,	,,	,,	1·08
,,	6	,, 24	,,	1,096		,,	,,	,,	1·25
,,	7	,, 36	,,	1,000		,,	,,	,,	1·15
,,	8	,, 48	,,	1,044		,,	,,	,,	1·20
,,	9	,, 72	,,	1,220		,,	,,	,,	1·38
,,	10	,, 96	,,	1,248		,,	,,	,,	1·39

Experiment II.—An exactly similar experiment was done upon a second healthy individual, 350,000,000 organisms of the *Micrococcus catarrhalis* being injected, with the following result :

TABLE IV.

Serum	1	before injection			942	cocci	in 200	cells.	Index = 1·00
,,	2	after 3	hours		722	,,	,,	,,	0·77
,,	3	,, 6	,,		580	,,	,,	,	0·62
,,	4	,, 9	,,		825	,,	,,	,,	0·88
,,	5	,, 15	,,	1,125		,,	,,	,,	1·20
,,	6	,, 22	,,	1,080		,,	,,	,,	1·15
,,	7	,, 28	,,	1,131		,,	,,	,,	1·20

In both of these experiments we see a very pronounced depression indeed produced in the index, in each case to the extent of 0·4. The duration of this depression was short, it is true, but no shorter than that obtained in a similar experiment upon an infected person, as is seen in—

Experiment III.—From the tracheal mucus and nasal secretion of an individual who had been suffering for a fortnight with a very bad tracheal cough a practically pure culture of the *Micrococcus catarrhalis* was isolated,

and the index found to be 0·56. An injection of 250,000,000 organisms was given, and the effect upon the index determined as follows, the index prior to injection being called unity :

TABLE V.

Serum	1	before injection			140	cocci in	100	cells.	Index = 1·00
,,	2	4	hours	after	90	,,	,,	,,	0·64
,,	3	8	,,	,,	220	,,	,,	,,	1·57
,,	4	12	,,	,,	280	,,	,,	,,	2·00
,,	5	15	,,	,,	312	,,	,,	,,	2·23
,,	6	18	,,	,,	325	,,	,,	,,	2·32

The chief difference is the much more pronounced subsequent elevation of index. To the depression of the index the term ' negative phase ' was given by Wright, while the subsequent rise he called the ' positive phase.' The negative phase thus comprises the interval when the index is falling, and also that when it is rising until the level at which it stood prior to injection is again attained. The full rise having been attained, the crest of the positive phase may be said to have been reached, as at seventy-two hours in Experiment I. and at fifteen hours in Experiment II. (*supra*). The index remains practically steady at this elevated level for a time, which varies in different individuals and for different organisms—it may be for hours, days, or even weeks. This may be termed the ' positive phase plateau.' It then begins to fall, and falls with a rapidity which also differs in different cases.

During the period of falling in the negative phase the patient may present marked clinical features. For instance, in cases of acne a fresh crop of pustules usually appears ; in cases of cold the cold gets worse ; in tubercular cases the patient may feel restless and ill or experience increased pain in a joint. Only rarely is the

temperature, pulse, or respiration markedly affected. Very soon indeed after the inception of the rise, even before the index has reached the level at which it stood prior to injection, the patient may begin to improve and declare himself to feel better.

A very marked instance of this was afforded in the case of a severe gonococcal conjunctivitis, in which the pain, discharge, and chemosis all diminished two days before the index had reached the level at which it originally stood. *The* factor in improvement would, therefore, appear to be a ' rising ' index.

It must, however, be mentioned that the above is not a complete description of all that occurs or may occur after the injection of a bacterial vaccine, and other variations may be introduced by modifications in the dosage.

Thus, it is probable that with a medium dose the first effect is a very slight and very transient fall indeed of the index, due to the immediate combination of the opsonin at the site of injection with anti-opsonin present in the vaccine. To this the body makes reaction by formation of fresh opsonin, with the result that there ensues a short period of slightly raised index, and it would appear that the improvement sometimes seen during the supposed ' negative ' phase is in reality due to this initial temporary rise.

After this oscillation the true negative phase begins, to be succeeded by the positive phase, though fresh oscillations may occur at any period.

With minimum doses of a vaccine, on the other hand, all oscillations and the negative phase itself may be elided. and injection be followed by an immediate rise, limited alike in extent and duration.

Buxton[1] has demonstrated the following important

[1] *British Medical Journal*, November 6, 1907, p. 1421.

difference in the behaviour of a normal and of an immunized animal to infection: In the former phagocytosis is weak and extracellular bacteriolysis strong; as a result of these two factors extracellular destruction of bacteria is great, and the consequent liberation into the circulation of the bacterial endotoxins is great, whereby severe reaction upon certain cells, such as those of the nerve centres, is produced. In the 'immunized' animal, on the contrary, phagocytosis is strong and extracellular bacteriolysis weak. The destruction of the bacteria, therefore, chiefly occurs intracellularly, and the endotoxins are destroyed before these can enter the general circulation, and so reach the nerve centres.

Duration of Negative Phase in Phthisis.

Lawson and Stewart[1] investigated the duration of the negative phase in 120 cases of phthisis. Their results were as follows:

No negative phase in 15 cases.
Persistent negative phase in 21 cases.
Negative phase lasting—

1,	2,	3,	4,	5,	6,	7,	8,	9,	10,	11,	12,	13,	14 days.
in 14,	12,	10,	5,	7,	4,	10,	4,	4,	3,	4,	1,	1,	5 cases.

Total: 84 cases.

The pulse and respiration did not appear to be affected at all, while the temperature showed no response during the negative phase in 50 per cent. of cases. It would thus appear that in 41 per cent. of the cases the negative phase lasted over a week. Upon the yet more important questions as to the interval occupied in various cases in attaining the crest of the positive phase and the duration of the plateau published information is lacking.

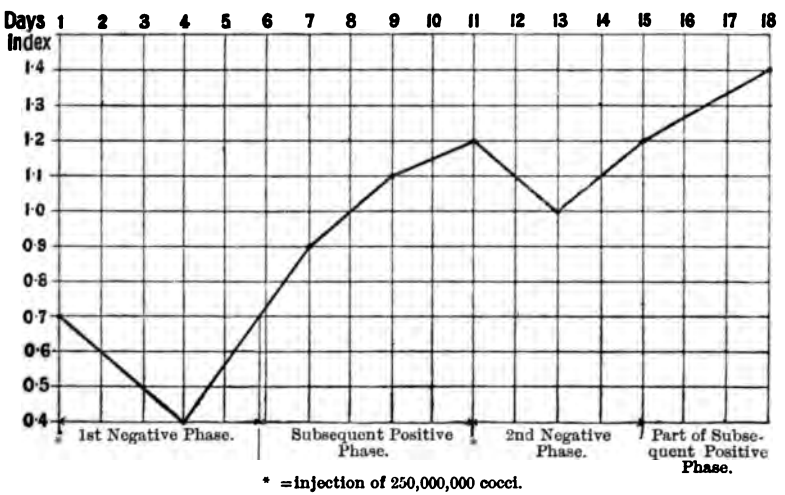
[1] *Lancet*, December 9, 1905, p. 1682.

The significance of a persistent negative phase after a first injection of tuberculin is great. It may mean that the case is one altogether unsuited to this course of treatment on account of the immunizing machinery having altogether broken down; it may mean that the initial dose was much too large, in which case it is unnecessary to wait any longer than until all constitutional symptoms have disappeared before reinoculating at this level with a much diminished dose; or it may be merely a peculiar phenomenon that the author has several times experienced, especially in chronic gonorrhœal cases. As subsequent events showed, the immunizing machinery was far from exhausted, nor was the dose too large, yet the index fell markedly, and there it remained for weeks at a new low level. The repetition of the original dose resulted in a perfectly satisfactory response, as did all subsequent injections. In these instances, then, it is probably good practice, except in obviously bad cases, to repeat the original dose a second time. A further fall and persistence of the negative phase would be warning to wait a few weeks and then begin again with a dose only a third or quarter as great as that previously employed. Yet, again, in cases which have been doing well and had several injections the usual dose will produce an unexpectedly long negative phase, lasting for three, four, or five weeks, although the patient apparently continues to improve. What this means I know not at all, but the safer course appears to be to wait overlong rather than to get impatient and inject prematurely.

THE CUMULATION OF NEGATIVE AND OF POSITIVE PHASES.

A second injection during a negative phase will result in further depression of the index to yet a lower level—that is, one negative phase may be superimposed upon another. The same holds true for positive phases, and this production of cumulated positive phases is the great aim in opsonic treatment, for in this way the index may be raised to a very high level. It still remains true, however, that the first result of an injection is to produce a negative phase, so that a slight lowering of the raised index at first results, to be followed by a further rise. This cumulation of postive phases may be thus shown diagrammatically (Chart I.) :

CHART I.



* =injection of 250,000,000 cocci.

It is generally held that this much-to-be-desired object is unattainable in the case of tuberculin injections ; that a cumulation of positive phases cannot be produced, and

that each injection is to be conducted as if a new case were being begun, except that gradually increasing doses are to be employed. While this is generally true, frequent determination of the index will sometimes enable the psychological moment to be seized, and a cumulation of positive phases to be produced. A few additional cases seem, again, to be especially predisposed to such a result.

In tubercular cases, then, it is customary to allow the good effects of one injection, produced by the resultant positive phase, to take full effect before again inoculating. This means, as a rule, an interval of about three weeks between successive inoculations. In other injections the aim always is to superimpose one positive phase upon another. To this end a fresh injection is given while the previous positive phase is still on, and the best time is coincident with the attainment of the crest or a day or two after, rather than when the index has again begun to descend.

Regulation of Dosage.

That doses of appropriate magnitude be employed is of importance secondary not even to proper spacing of the several inoculations. Experience has shown that the proper initial dose varies considerably for different organisms and to a less extent for different persons. The average initial dose for each organism is given later. Let us suppose that this dose has been given in a certain instance, the index prior to inoculation having been found to be subnormal. A fresh determination of the index is made twenty-four hours after injection, and again seven or ten days later.

The various possible results and the deductions therefrom may be thus displayed schematically :

Index 24 Hours after Injection.	Index 7 or 10 Days Later.	Deduction.
Slight fall.	Further fall.	Dose too large.
Slight rise.	But little altered.	Dose too small.
Slight fall.	Marked rise.	Dose correct.

It will be found, as treatment progresses, that gradually increasing doses, often at shorter intervals, have to be employed to produce any marked effect upon the index. Thus, in staphylococcal cases the initial dose of 250,000,000 organisms may have finally to be increased even to 5,000,000,000 before a cure is effected. So long as a certain dose produces an adequate response increase of it is not advisable, but so soon as this result is not achieved the indication for doubling the dose is present. The approaching termination of infection is indicated when these large doses finally fail to produce a rise of more than one or two decimal points in the index, which assumes a level at unity or slightly above it. One or two more large doses are then to be followed by diminished doses at increasing intervals.

Other Methods of Raising the Opsonic Index.

Injections of bacterial vaccine are not the sole means whereby the opsonic index may be raised. Applications of heat and massage probably have their good effect by acting locally in this manner.

It has been shown that Bier's treatment by passive congestion has the effect of raising the general opsonic power of the blood to an infecting organism, while nuclein injected subcutaneously and yeast by the mouth (Huggard

and Moreland[1]) have a similar action. This explains the well-known therapeutic action of yeast in erysipelas, furunculosis, and acne, and the varied results obtained by its administration uncontrolled by the opsonic index.

Malden[2] showed that its action was probably due to the nucleo-albumins it contained.

It has been already mentioned that the administration of antidiphtheritic serum produces a temporary fall in the tuberculo-opsonic index, which is followed by a subsequent rise.

Bosanquet and French[3] studied the effect of Marmorek's antituberculous serum upon the tuberculo-opsonic index in five cases. They found that, when given subcutaneously in one case, an alarming fall in the index from 1·05 to 0·25 occurred; cessation of the injections was followed by a rapid rise to 1·45.

In the other four cases the rectal method of administration was followed. In three of these a rise in the index was produced, usually after three or four daily doses had been given. A maximum index was soon reached, and continued with slight oscillations for three or four weeks while the serum was being given, and for about a week subsequently. In the fourth case, which was a very advanced one, the index fell from 1·75 to 0·8 during treatment, recovering subsequently slowly to 1·0.

It would thus appear probable that in certain instances the beneficial results of antisera may be, at all events, partly due to the elevation produced in the opsonic index.

[1] *Lancet*, June 3, 1905.
[2] *British Medical Journal*, July 1, 1905.
[3] *Ibid.*, April 13, 1907, p. 862.

Elevation of the Opsonic Index not the Sole Necessity.

Wright has been at especial pains to point out that the successful combat of bacterial invasion does not depend upon elevation of the opsonic index alone. Increase in the bacteriotropic substances of the blood having been secured, it still remains to insure that these be brought in sufficient amount to the point of attack. Experiment has shown that the fluid portion of pus may be entirely free from opsonin, while the amount of the latter in the serous exudates in pathological conditions of the peritoneum, meninges, pleura, and pericardium may be very greatly diminished. It therefore becomes necessary to insure the removal of the fluid poor in antibacterial substances, and its partial replacement by lymph rich in such substances. This end is secured in various ways, as by opening a fluctuating abscess, doing a laparotomy upon a tubercular peritonitis, or tapping an empyema. Other cases there are, such as more or less non-discharging sinuses, where dense granulation tissue and deposits of fibrin prevent free access of lymph, and brawny swellings where the same result is brought about by blockage of the lymphatics. The former of these conditions Wright meets by the introduction into the sinus of a solution of 0·5 per cent. citrate of soda and 5 per cent. sodium chloride, the former decalcifying the lymph, and so preventing its coagulation, the latter by osmosis causing transudation of fluid from the vessels.

The surgeon has been wont to secure a similar result by scraping and the application of caustics. Brawny swellings are to be freely incised, and the coagulability of the lymph diminished by three-hourly doses of 60 grains of sodium citrate. Further consideration is given to this question in later pages.

CHAPTER III

DETERMINATION OF THE OPSONIC INDEX

Definition of the Opsonic Index.

The opsonic index may be defined as the ratio :

$$\frac{\text{Opsonic content of unit volume of the patient's blood-serum}}{\text{A normal person's}}.$$

This is now determined according to a method first introduced by Leishman for the estimation of the phagocytic power of blood. Other methods have been employed, but need not be referred to, as they have been completely superseded by Wright's modification of the above.

The following materials and apparatus are required :

1. A sufficient quantity of the patient's blood-serum and of that of the normal person.

2. Blood-cells which have been thoroughly freed from the plasma in which they normally float.

3. An emulsion of the bacterium towards which the opsonic index of the patient is to be determined.

4. Glass-tubing $\frac{3}{16}$ inch and $\frac{5}{16}$ inch in external diameter —the smaller for collection of the blood samples, the larger for the opsonic determinations. The former are to be cut into lengths of about 3 inches, and drawn out into capillary threads at each end, which are then cut off short. The latter are to be drawn out at one end only into fine capillary threads about 6 inches long and as far as possible of uniform bore.

5. Strong rubber teats, file, grease pencil.

6. Centrifuge with hæmatocrite attachment, and glass tubes to fit the same.

7. Watch-glasses and platinum loop.

8. The following solutions in sterile distilled water, carefully freed from dust and hairs, not by filtering, but by centrifugalization :

(*a*) 1·5 per cent. to 2 per cent. neutral sodium citrate.

(*b*) 0·8 per cent. sodium chloride.

(*c*) 0·1 per cent. sodium chloride.

9. Glass slides thoroughly grease-free.

10. Incubator (Hearson's biological), maintained at 37° C.

11. Methylic alcohol for fixing.

12. Appropriate staining solutions—viz., for all organisms except tubercle, Leishman's stain ; for tubercle, carbol fuchsin, 20 per cent. sulphuric acid, absolute alcohol, and toluedene blue.

13. Porcelain jar with metal cover for holding slides during fixing and staining.

14. Microscope with $\frac{1}{12}$-inch oil-immersion lens and mechanical stage ; cedar-wood oil.

The following procedure is then to be adopted :

1. *Collection of Blood for Serum.*—This is done by cleansing the finger-tip or lobe of the ear with warm soap and water or 2 per cent. lysol solution, drying, and rubbing well with a small piece of lint saturated with ether. When the latter has evaporated, a prick is made with a needle. This is best done decisively, for patients prefer one effective puncture to several ineffective ones. As a rule they prefer the finger-tip to be utilized, but

should the epidermis be obviously thick at the root of the nail, it is better to employ the lobe of the ear. The blood must flow spontaneously, or but very slight pressure be employed, and the first drop wiped away, for, as has been shown, the opsonic content of the plasma of muscle and the subcutaneous tissues is considerably higher than that of the blood. On approximating one of the capillary ends of the tube to the blood, the latter will flow spontaneously into it. Three or four drops of blood will suffice. The tube must now be sealed off, and here a word of caution is necessary. Opsonins are readily destroyed by heating to 60° C. ; the blood must, therefore, not be heated. All risk of this is avoided by gently warming the end of the tube away from the blood, and then sealing off this end. Lay the tube down flat, and allow it to cool. In doing so the blood is sucked back from the unsealed capillary end by the vacuum produced by the contraction of the contained air as it cools. When this has occurred, that end also may be sealed off in the tip of the flame. These precautions are far from unnecessary, for I have seen many samples of blood quite spoilt in the collecting.

2. *Preparation of the Blood-Cells.*—It matters not whence the blood for this purpose is collected provided not from a sufferer from disease of the lymphatic system ; or from an individual whose red blood-cells are capable of agglutination either by their own serum or by that from any other source. As Fleming[1] has pointed out, this is particularly liable to occur in the case of infected individuals, and the effect of agglutination of the red cells in an opsonic mixture is to give an unduly high phagocytic count.

[1] *Practitioner*, May, 1908, p. 607.

The blood should be collected aseptically to prevent contamination with organisms which will grow rapidly in such a favourable medium, and prove troublesome, perhaps, when the time comes for counting the slides. The collection is done in one of the $\frac{5}{16}$-inch glass pipettes, to which a strong rubber teat has been fixed. A little of the sodium citrate solution is first sucked up to prevent coagulation, then the blood, which is at once transferred to a tube containing more of the sodium citrate solution. Blood may be added to the citrate in the proportion of 1 to 5.

The citrate, by precipitating the calcium salts of the blood, effectually prevents coagulation. The citrated blood is now transferred to the centrifuge tubes and thoroughly centrifugalized. A very considerable speed —10,000 revolutions per minute—may be advantageously employed ; the corpuscles will be thrown down quickly, and yet escape damage. It is to be remembered that the white cells are lighter than the red, and will therefore be thrown down last. It is well to continue the operation till a distinct white layer is seen lying upon the layer of reds, for efficient centrifugalization means numerous white cells, and so greater facilities in counting. The clear supernatant citrate solution is pipetted off, care being taken not to disturb the white layer. Some of the 0·8 per cent. sodium chloride solution is now added to the cells, and these thoroughly mixed up with it and again thrown down. Concentration of the white cells may be effected by removing the upper layer of cells from one tube, adding these to the second tube, the lower layer in the first being then thrown away. The washing with normal saline solution is repeated once or twice. As much of the liquid as possible is finally removed ; the

cells, thoroughly mingled with what is left, are then ready for use. A little plug of cotton-wool will prevent access of organisms from the air.

3. *Preparation of the Bacterial Emulsion.*—This, with one exception—that of the tubercle bacillus—has always to be prepared fresh. Young organisms stain better and more uniformly than old. It is, therefore, better to employ as recent a culture as possible, especially in the case of such organisms as that of Morax-Axenfeld, which begin to involute even before eighteen hours. A twelve- to sixteen-hour-old culture on an appropriate medium—such as agar for staphylococci, streptococci, coli, etc.; blood-agar for gonococci; nutrose ascitic agar for *Bacillus Morax-Axenfeld* or *Micrococcus catarrhalis*—is, therefore, to be employed. If the growth be a very copious one it is best to take a loopful of the culture on a platinum wire, and carefully emulsify it in a watch-glass with a little of the 0·1 per cent. NaCl solution. If the growth be scanty, then it is best to pour a few drops of the solution into the culture-tube and emulsify it *in situ*. The turbid emulsion thus produced contains many clumps, which are to be thrown down by means of the centrifuge. A minute or two will usually suffice at a high speed, but experience alone will teach just how long it should be continued. In any case, it must be efficient, for nothing is more annoying than to find clumps in the films when everything has been completed, for if accuracy be desired the whole process must then be repeated. Experience, again, alone will teach whether the emulsion requires further dilution. The opacity of an emulsion, say, of gonococcus must be much greater than that of emulsions of staphylococci or Friedländer's bacillus in order to give the same count in the normals. A strength which will

give a count of about 250 to 350 bacteria in the 100 cells of the normal should be aimed at. In the instance of the tubercle bacillus an emulsion once made and found satisfactory may be preserved sealed up in capillary tubes for practically any length of time, especially if the bacteria have been killed by heating to 70° C. for one hour. When wanted, all that is necessary is thoroughly to shake up the emulsion and give it a few sharp turns in the centrifuge to throw down any clumps which may be present.

These preliminaries over, we now take as many of the fine long-drawn capillary pipettes as there are sera to be investigated. They should be chosen of as equal bore as possible. It is advisable for them to have been sealed off at the fine extremity, plugged with cotton-wool at the other, and dry sterilized. The fine ends are cut off square by means of a file scratch, and marks made with a grease-pencil about 1 centimetre from the ends. The content as far as this mark is the unit volume in each case. To the plugged ends are fitted the strong rubber teats, and each pipette is marked with a number corresponding to a serum. The rubber teat is now held between thumb and forefinger and gently compressed, the capillary end inserted into the well-mixed blood-cells, and the unit volume drawn up by slightly relaxing the pressure on the teat. Next a tiny bubble of air is allowed to enter, a second and third volume of blood-cells being drawn up in similar fashion, each separated from the next by a bubble of air. A volume of the bacillary emulsion is now drawn in with especial accuracy, then a bubble of air ; finally, 2 volumes of the serum, which must be taken up free from admixture with red cells, as these tend to produce an unduly low phagocytosis. We thus have in order in the pipette 3 volumes of blood-cells, 1 volume of emulsion,

2 volumes of serum, each volume being separated from the adjoining by means of a bubble of air. This is the procedure usually followed, but if the emulsion be suspected to be too thin, then 2 volumes of blood-cells, 1 volume of emulsion, and 1 of serum may be employed, or the original 1, 1, 1 of Wright. The order—cells, emulsion, serum—should, however, always be followed, for in this way contamination of the cells by the bacterial emulsion, or introduction of opsonin from the serum into the emulsion, is avoided. By gentle pressure on the teat the several volumes are expressed on to a clean glass slide, and thoroughly mixed by alternately sucking the mixture into the pipette and squeezing it out again upon the glass slide. Only by thorough mixing can a satisfactory count be ultimately obtained. The mixture is finally withdrawn as completely as possible some little distance into the pipette, and the extremity sealed off in the flame.

This operation is repeated with each serum. The several pipettes, carefully labelled, are then placed in the incubator at 37° C. for fifteen minutes. By means of a file-scratch the ends are then cut off, the content of each blown out on to a clean glass slide, and very carefully mixed. Half the drop is then transferred to a second slide, and two blood-films prepared by the slide method—*i.e.*, by drawing the extremity of one slide held at an acute angle over the surface of the other upon which the drop of blood has been placed.

Mention may here be made of two points of some importance: Firstly, the thickness of the blood-film depends partly upon the pressure employed in the spreading, and to a greater extent upon the inclination of the moving slide to the stationary one. The more

vertical the former is held the thinner the film, and, conversely, the more acute the angle the thicker the film. Now, the ideal film is one in which the corpuscles do not lie one upon the other, but are even separated by distinct intervals, for in such an one the white blood-cells flatten out, and consequently are of larger size. The contained bacteria are, therefore, much more easily distinguished after staining, and counting is consequently facilitated. Films containing tubercle bacilli may, however, be spread rather thicker than in the case of other organisms, for the staining methods are more drastic, the organisms show up more clearly, and the red cells are practically invisible.

To obtain the best films firm pressure should, therefore, be employed, and the slides should be held at an angle of 60 degrees to one another.

Secondly, owing to their greater viscosity, the white cells tend not only to be drawn towards the end of the film, but also to run to the edges. These facts may be turned to practical advantage if the precaution be taken not to place too large a quantity of blood upon the slide. Instead of using a slide of ordinary breadth for spreading, one may be bisected longitudinally by means of a glazier's diamond, and this half-slide employed. If the drop of blood be then placed at the mid-point of the breadth of the slide, but near one extremity, and the half-slide used as a spreader, a film is obtained with two edges lying some little distance from the margins of the slide, and along these edges the white cells will be found collected. Next, by moving the spreader in a series of little jerks instead of with a uniform motion, a number of little valleys, as it were, are made in the film, in which the white cells collect just as they do along the edges.

Attention given to these trifling details is well repaid by the additional ease with which the slides are counted.

The films, having been spread, are then allowed to dry in the air. One of each is reserved in case of accident; the others are treated as follows: If containing tubercle bacilli, they are then fixed for fifteen minutes in methylic alcohol, or for one hour in a mixture of equal volumes of ethyl alcohol and ether, stained by the Ziehl-Nielsen method, and counterstained with toluedene blue. Five minutes' application of the latter stain, followed by thorough washing under the tap, will show up the bodies of the white cells most effectually. For any other organism than the tubercle bacillus the films are best stained according to Leishman's method.

Next, with $\frac{1}{12}$-inch oil-immersion lens and a mechanical stage the numbers of bacteria contained in each consecutive five polymorphonuclear leucocytes are noted till 100 cells have been counted. No estimation can be considered satisfactory unless the numbers of bacteria found in each five cells approximate to each other. The following points may here be noted, and too much stress cannot possibly be laid upon their importance if accuracy be desired in the estimation: Firstly, the advisability of counting as many cells and their bacterial contents as possible. Reliance is commonly placed upon a count of fifty cells. I would maintain that no amount of care at every stage will insure an accurate result with such a count; 100 cells is the minimum number that should be observed. Secondly, the occurrence of bacterial clumps of any size in a film, especially if these lie upon any of the cells, should damn such a film beyond redemption. There is nothing for it but to repeat that experiment with that serum, and, of course, with a fresh normal.

Thirdly, the occurrence of clumps of leucocytes, especially if these be held together by threads of fibrin, should render the experiment null and void. Once more repetition is more than advisable. Of course, both these last difficulties should not occur. They are, as a rule, the result simply of lack of care in preparing the blood-cells and the bacterial emulsion.

The determination of the index is now completed as follows : The normal serum is taken as having an opsonic index of unity. The number of bacteria found in 100 cells of each of the patient's slides divided by the number in 100 cells of the normal slide gives their respective indices. To recapitulate, then, the points of importance, by observance of which accuracy can alone be secured and much time and trouble saved :

1. The solutions used for the preparation of the blood-cells must be quite free from hairs and filaments, for these inevitably entangle the white cells and lead to clumps in the films.

2. The blood must be received into sufficient citrate solution to insure complete prevention of clotting, and the cells, when washing is complete, must be thoroughly mixed to insure equal numbers of leucocytes in equal volumes.

3. The bacterial emulsions must be thoroughly centrifugalized to free them from all clumps, and growths of not more than eighteen hours should be employed for their preparation. The strength should be such that 250 to 350 bacteria are found in 100 cells of the normal.

4. The several volumes must be thoroughly mixed, both before and after incubation, to secure uniformity of count in each series of five cells.

5. The films must be spread thinly to insure the polymorphs being as large as possible.

6. Staining must be satisfactory, and the cell-body shown up. If this prove not so, the reserve slide must be stained.

7. At least 100 cells in each film should be counted.

8. If at the first attempt an unsatisfactory result is obtained, whether from clumps of cells or bacteria, or from too few white cells being present in the films, perseverance in counting imperfect films is to be deprecated. Time and temper will alike be saved by repeating the whole estimation.

Brief reference may here be made to recent attempts at shortening the technique in determinations of tuberculo-opsonic indices by the employment of emulsions of killed organisms which have been already stained with carbol fuchsin. Although one or two observers[1] have reported favourable results, the more general experience is that accuracy cannot be thereby secured. The chief difficulty appears to be in the preparation of a satisfactory emulsion free from clumps. Staining, whether by weak and cold or hot and strong fuchsin solutions, seems to affect the organisms in such a way that centrifugalization, which throws down the clumps, also suffices to throw down the single bacilli.

The Question of the Accuracy of this Method of Estimating the Opsonic Content of the Blood.

It must be admitted that the reliability of estimations of the opsonic content of the blood, conducted according to the above technique, or slight modifications of it, has

[1] Campbell, *British Medical Journal*, April 13, 1907, p. 866.

been rudely assailed during the past two years—among others by Simon, Lamar, and Bispham,[1] and by Walker[2] in America, and by FitzGerald, Whiteman, and Strangeways[3] in England.

In these un-Socratic days the honesty of all, both of those upholding and of those opposing any given procedure, is to be assumed. Against their experiments and results, then, are to be placed those of Wright and his co-workers, Bullock, White,[4] the author, and many others. Upon the one hand are those who obtain unreliable results; upon the other those who truly believe, and, as far as figures can substantiate a belief, find support in their figures for the belief, that in their hands the method affords reliable results.

It thus follows that there are two classes of observers: (1) those who can estimate an index accurately by these methods; and (2) those who cannot estimate an index accurately by these methods—just as there are surgeons who can perform perfectly the delicate operations advocated by Mayo Robson and by Arbuthnot Lane, and others who cannot. Upon the one hand, the possibility of the proper performance of these operations cannot be impugned by any multiplicity of ill-results in unskilled hands; upon the other hand, the possibility of the accurate estimation by this method of the opsonic content of the blood is not disproved in the slightest by any number of inaccurate estimations in unskilled hands.

Let me not be misunderstood. I make no claim that

[1] *Journal of Experimental Medicine*, August, 1906, p. 651; *Ibid.*, September, 1907, p. 485.

[2] *Journal of Medical Research*, July, 1907, p. 521.

[3] *Bulletin of Committee for Study of Special Diseases*, Cambridge, vol. i., No. 8.

[4] *Practitioner*, May, 1908, p. 639.

the accuracy of the method is comparable with that, say, of the determinations of the various physical coefficients. There are pitfalls innumerable for the unwary, and even the most skilled experimenter will every now and again obtain a wrong result; but here is an important point: he will know that he is obtaining an unreliable result, and will either repeat the whole estimation or count a much larger number of cells than usual, and so minimize the error. Fleming (*v.s.*)[1] appositely remarks: 'In this connection it should be pointed out that it is a great mistake to have any arbitrary number of leucocytes which one counts, neither counting more nor less, whatever the conditions may be'—a remark with which I most completely agree; and again: 'Intelligence must be brought to bear on the subject in hand.'

Despite this, it cannot but be admitted that even in the hands of the most skilled there is, as Greenwood[2] points out, an error inherent in any such method which is quite inevitable—an error, however, which only rarely exceeds 10 per cent., and is usually about 5 to 6 per cent., and is of little or no practical importance.

Other Methods of Estimating the Opsonic Content of the Blood.

Inasmuch, then, as the above method of determining the opsonic index must be admitted to be a very delicate and somewhat laborious and difficult matter, and one, moreover, which is unsuited to a certain proportion of workers, any other method which is less laborious, less difficult, and suitable for all, can only be regarded as in the highest degree desirable.

[1] *Practitioner*, May, 1908, p. 627. [2] *Ibid.*, p. 641.

Several attempts have been made in this direction. Thus, Simon (*v.s.*) would substitute an index obtained by diluting the blood in varying proportion (ten to thirty times), and after incubating with a bacterial emulsion of considerable strength, comparing the percentage of phagocyting leucocytes in the specimen of blood under investigation with the figure obtained after a similar procedure with a specimen of normal blood. This he calls the 'percentage index,' and finds it sometimes to agree well with the opsonic index, sometimes to differ considerably from it, in which event he prefers to follow the guidance of his percentage index. As to the accuracy of the method I can offer no opinion, but it is admittedly even longer than the method it seeks to displace, and to my mind has this very grave objection: the dilution of the serum. It is perfectly true that if the opsonizing power of the serum of an injected individual be compared with that of the serum of a healthy individual, marked differences are revealed according as the undiluted sera or the sera in various degrees of dilution are compared. As dilution proceeds, it will sometimes be found that the opsonizing power of the immune serum rapidly falls off in comparison with that of the normal serum. Thus, an index of 1·4 may be obtained for the undiluted immune serum, and an index of only 0·8 for the same serum in a dilution of 1 in 20. Certain observers—as Simon and Walker (*v.s.*), who estimate the opsonic index by means of diluted sera—consider examination of such to afford the better idea of the immunizing power of the blood. I would maintain that they are conducting an investigation—the results of which are doubtless of value—under conditions which do not in the least obtain in any pathological condition in the

human organism. If possible, what one desires to ascertain is the opsonizing power, not even of the blood-serum, but of the blood-plasma, in the condition in which it actually is in the human organism. Moreover, not even in a suppurating focus nor in an exudate of pus do the bacteria ever present any such ratio to the phagocytes as they employ in their phagocyting mixtures. In order to learn the immunizing response of the body, say, in a case of streptococca septicæmial, where, perhaps, ten streptococci can be isolated from 5 c.c. of blood, they would present an emulsion containing at least 5,000 million organisms per c.c. to a mixture of blood-cells containing, perhaps, 5,000 to 10,000 phagocytes per c.c. in a serum diluted twenty or thirty times. Can any conditions less like these obtaining in the human organism easily be conceived ?

The method suggested by Stewart,[1] Dodds,[2] and Veitch[3] has, on the other hand, much to recommend it, and most nearly of all approaches the natural conditions. It is conducted as follows : One volume of blood is withdrawn from the patient in a sterilized capillary pipette, and at once thoroughly mixed with an equal volume of 1·5 per cent. solution of sodium citrate in 0·8 per cent salt solution, and the ends of the pipette sealed. The same is done with the control normal blood. These mixtures are then preserved till required, and, according to Stewart, keep unaltered for twelve hours, or, if kept in a refrigerator, for three days.

The phagocytic mixture is made by taking two volumes of the blood citrate mixture and one volume of the

[1] *Journal of Bacteriology*, 1908.
[2] *British Medical Journal*, October 12, 1907, p. 948.
[3] *Journal of Pathology and Bacteriology*, January, 1908, p. 353.

bacillary emulsion, and proceeding in the usual way. The hæmophagocytic index thus determined is claimed to agree well with the opsonic index, while the method affords a certain saving of time, especially when only two or three bloods have to be examined, and is perhaps more accurate, inasmuch as clumps of leucocytes very rarely occur. The fact that the plasma is employed instead of serum, and the patient's own leucocytes, which are not altogether an indifferent factor, are additional recommendations.

CHAPTER IV

PREPARATION OF THE VACCINE

THE general consensus of opinion is that the best possible results are, as a rule, only to be looked for when organisms isolated from the patient's own lesion are employed for the manufacture of the vaccine. Several considerations may, however, militate against the advisability of this procedure. The chief of these are as follows :

1. Where the isolation of the organism is so difficult and tedious that the resultant loss of time would fail to compensate for the advantages obtained. An excellent example of this is afforded in tubercular affections. Here we are compelled to resort to inoculation experiments, the animals usually selected for the purpose being the rabbit or guinea-pig, and the site of inoculation either the subcutaneous tissue of the groin of the latter or the anterior chamber of the eye of the former. Of these two animals, the guinea-pig is generally held to be the more susceptible to the tubercle bacillus, dying of general tuberculosis from six to ten weeks after inoculation, according to the virulence of the organism and the number introduced. On the other hand, if tuberculous material be introduced into the anterior chamber of the eye of the rabbit, an iritis which is almost pathognomonic results in from two to four weeks. In either case the loss of time is very considerable. Nor is this all. The growth of the tubercle bacillus is again so slow, and the preparation of

tuberculin so difficult an operation, that another two or three months would be consumed in the preparation of the vaccine. This is very greatly to be regretted, for many of the only partial successes or even failures in cases treated by tuberculin are possibly very largely due to the employment of stock tuberculin. This question will be again referred to later.

A second example of this class of case is afforded in some chronic gleets. The gonococcus may be visible in smears of the urethral secretion, yet, despite the utmost care in taking the cultures, it may prove impossible to free the gonococcus from the contaminating organisms.

2. The infection, although localized, may be of so acute and destructive a type that the loss of even two or three days may be of vital importance. An excellent example of this is seen in gonorrhœal conjunctivitis in the adult. Here prompt injection of a stock vaccine is obligatory immediately the patient is diagnosed. I have seen cases so severe that total destruction of the sight was inevitable in two or three days, thereby completely held in check, and, save for the destruction which had already occurred, cured within a week (*vide* chapter on The Eye).

3. Where the infection is so very chronic that it is reasonable to suppose that the virulence of the infection has been greatly reduced, though even here it is better wherever possible to test the virulence by an inoculation experiment upon animals. Good examples of this class of case are afforded by—(*a*) very chronic cases of osteomyelitis which have been subjected to considerable surgical treatment; (*b*) chronic gonorrhœal infections, especially old gleets in the male, and tubal cases in the female.

4. A final exception may be made in the instance of such organisms as seem to be definite entities, and not to

compose a family group of such closely related members as the streptococci. So far as we are aware, there is, for example, but one *Bacillus septus* and one *Micrococcus melitensis;* yet even here the better plan is undoubtedly the preparation of a special vaccine, unless other considerations are against the adoption of this plan.

The method employed for the isolation of the organisms will vary according as to whether we are dealing with a pure or a mixed infection, and this point may be largely determined by first making smears, staining by Gram's method and with methylene blue, and examining microscopically.

Should the infection appear to be unmixed, then cultures are to be made at once upon the medium best suited for the growth of the organism in question, such as blood-agar in the case of pneumococcus, nutrose ascitic agar or blood-agar in the case of gonococcus, agar in the case of staphylococcus, glycerine potato in case of tubercle. If the infection be a mixed one, it must be borne in mind as a most important point that the isolation must be done as quickly and in as few subcultures as possible, for only thus is a fully virulent growth likely to be obtained. Of any peculiarities of growth of an organism in presence of others advantage is therefore to be taken, and cultures made from the infected part with every possible care.

A few details which have been found useful may here be given.

Tubercle Bacillus.

The tubercle bacillus is mentioned because the author feels convinced that more and more will it be found advantageous in difficult cases to continue injections

with a stock tuberculin only while a special one is in process of manufacture.

The peculiarity of localized tubercular affections is the paucity in the number of bacilli present. This holds true whether it is the pus from the tubercular joint or the tissues of a tubercular gland or conjunctiva. In the case of tubercular bladders and kidneys, however, very large numbers of bacilli may be discharged in the urine. Some means must therefore be adopted not only of freeing the tubercle bacilli from contaminations, but also for increasing their numbers. This is done, as said before, by inoculating a rabbit or guinea-pig. If the material be pus or solid gland, this is done directly ; if conjunctiva, care must be taken to cleanse the eye thoroughly with sterile saline before removing the piece of conjunctiva; if pus in urine the bacilli are to be separated by thoroughly centrifuging the urine which has been drawn off with a catheter, washed well with sterilized water, and again centrifuged, repeating this several times. The final deposit may then be employed like any other inoculum. Immediately the animal has died, or as soon as caseous glands are to be felt, or after three to four weeks in the case of injection into the anterior chamber of the eye of the rabbit, death is produced by means of chloroform ; the animal is opened with all antiseptic and aseptic precautions, and culture-tubes of glycerinized potato inseminated with as large portions of the diseased glands or iris as is possible. The tubes are then sealed up and incubated at 37° C. for six to eight weeks, when a copious growth of tubercle bacilli should be available for the manufacture of tuberculin. Unfortunately, there are cases where the tubercle bacilli thus obtained, often in considerable numbers, from the glands and spleen of

the injected animal refuse to grow in artificial cultures. The following modification of an old method has been given me by Williamson as very useful in obtaining cultures direct from sputum : A suitable lump is chosen, washed thoroughly in sterile salt solution, and incubated at 37° C. for ten to fourteen days with pure glycerine in the portion of 1 part of sputum to 4 parts of glycerine. The mixture is then employed for the insemination of broth, potato, or agar.

Staphylococcus Albus and Aureus.

(*a*) In cases of acne, furunculosis and sycosis are generally present in a state of purity, but often in limited numbers. It is not, therefore, advisable to do more than wash the surface of the skin with warm soap and water. The pus should then be carefully expressed from a solid pustule, if possible, for the softer ones may prove sterile, and a series of two or three sloped agar-tubes inseminated with varying amounts of the pus, and incubated for twenty-four hours at 37° C. A colony may then usually be picked out and employed to plant the required cultures.

(*b*) In cases of periostitis and osteomyelitis the infection may be a mixed one, when it is perhaps advisable to mix up some of the pus with a tube of broth and use some of this, either directly or after twenty-four hours' incubation, to make a series of agar-plates, from which a colony may then be selected.

Streptococcus.

The range of utility of streptococcal vaccines will be considered later ; suffice to say here that cultures may have to be obtained from pus, fibrinous exudate, or the

blood. Should microscopic examination of films reveal no organisms other than streptococci, cultures may be made at once upon agar; otherwise agar-plates must be made from some of the material after mixing it up with broth. I have found it highly advantageous in these cases to incubate the broth mixture for twenty-four hours at 37° C. before preparing plates. On agar streptococci grow much more slowly than other organisms, especially staphylococci, whereas in broth this is not only not the case, but the streptococcal colonies also tend to fall to the bottom of the broth. Slight centrifugalization accentuates this tendency. The supernatant liquid may then be poured off, and agar-plates prepared from the concentrated streptococcal emulsion. A colony having thus been isolated, subcultures are to be made upon sloped agar-tubes. The growth after eighteen to twenty-four hours is so slight that several tubes must be employed. A better way is to employ agar-plates inseminated by means of a glass rod, as the surface for growth is thus greatly increased.

If cultures are to be made from the blood, it is necessary to withdraw quite a considerable quantity—about 5 c.c. —from one of the large veins in the antecubital fossa. The skin is thoroughly washed with warm soap and water, and then with sterilized water. A bandage is applied tightly well above the elbow. Into a 10-c.c. syringe which has been well boiled about 1 c.c. of sterilized 2 per cent. sodium citrate solution is introduced to prevent clotting in the needle. The vein is then punctured in a direction against the venous flow, when the blood will at once flow into the syringe, which can then be filled. Three culture-tubes, each containing 10 c.c. of broth, are taken. Into the first 2 c.c., into the second 1 c.c., into the third 0·5 c.c.

are then introduced; they are well shaken up and incubated at 37° C. for twenty-four hours. The blood clots in a few hours, the pigment sinking to the bottom of the tube, leaving a translucent jelly-like clot suspended in the broth. In this clot the colonies develop as isolated masses, which may be easily removed by means of a pipette and used to inseminate agar tubes or plates.

Gonococcus.

This very delicate organism may require particular care in isolation. In cases of gonorrhœal conjunctivitis it is, however, present in a state of practical purity. It is only necessary to wash the eye out with sterilized water. After waiting a few minutes, the eye being kept closed in the meanwhile, small quantities of the exudate may be taken up with a sterilized platinum loop and used to inoculate sloped tubes of blood-agar; or, better still, plates of blood-agar may be inseminated by means of successive strokes of one or two loopfuls of the exudate. In this way distinct colonies are usually to be seen after twenty-four to thirty-six hours' incubation at 37° C. In urethral cases it is always well to take particular pains in cleansing the external meatus. The penis is held just behind the glans, the external meatus being held closed. The whole of the glans is then well cleansed with warm soap and water, then with weak antiseptic, finally with sterilized water. Any pus in the extremity of the urethra is then squeezed out and wiped off with damp sterile wool. The pus from farther back is then expressed, received upon the platinum loop, and used to plant cultures as before. In chronic cases it may be necessary to pass the loop a little way into the urethra. It is in these cases

well to remember that the larger number of cocci are to be found in the thin serous discharge rather than in the grumous. Sometimes, despite all care, numerous attempts will fail to isolate the gonococcus in very chronic cases. It only remains then to employ a stock vaccine.

A colony of pure gonococci having been isolated, fresh cultures are now to be planted. For this purpose we have the choice of two media. Freshly prepared blood-agar made with human blood, which is thoroughly mixed up with the agar and tints it a bright red. The medium should be quite moist, and is much superior to the similar preparation made with rabbit's blood. As an alternative nutrose ascitic agar is slightly inferior, but distinctly valuable. It consists of 2 per cent. agar, to which an equal bulk of ascitic fluid is added, and 2 per cent. nutrose. It is somewhat difficult to prepare, owing to the insolubility of the nutrose. Once made, however, it keeps very well. Personally, I now always use human blood-agar. The cultures are incubated at 37° C. for eighteen hours.

Pneumococcus

also grows best on human blood-agar. If successive strokes be made either upon blood-agar slopes or plates, a pure culture can usually be obtained at the first attempt, especially from an empyema or otitis media, and in eye cases if the eye has been well washed out previously with sterilized saline. In pneumococcal endocarditis cultures must be made from the blood in exactly the same way as described for streptococci, with the additional insemination of a tube of agar, by allowing a few drops of the blood to run over its sloped surface. From sputum its recovery is more difficult, and is best done by inserting

a small piece of sputum, which has been well washed several times in sterile saline solution, under the skin of a rabbit or mouse. In about forty-eight hours the animal will die with numerous capsulated cocci throughout its blood. Some of the heart-blood is then taken, with aseptic precautions, and allowed to run over the surface of tubes of sloped agar. In twenty-four hours numerous small transparent colonies, like drops of dew, appear. So rapidly does this organism lose its virulence, and therefore its value for the preparation of a vaccine, that even in four or five days after isolation from an animal's body its pathogenicity is already diminished. It is, therefore, especially necessary in the case of this organism that a first subculture should be employed for a vaccine. As in the case of the gonococcus, the cultures should be made on human blood-agar and incubated for between eighteen and twenty-four hours at 37° C.

Bacillus Coli Communis

may be present in a state of purity in appendical and extraperitoneal abscesses, in suppuration round the bile-ducts, in endocarditis, abscesses around the kidneys, and in the Fallopian tubes. It also occurs as a mixed infection in inflammation of the urinary passages, cystitis, and pyelitis. Its isolation is a very easy matter by means of agar, or, better still, plates of MacConkey's medium (which consists of 2 per cent. agar, 2 per cent. peptone, 0·5 per cent. bile salts, and 2 per cent. lactose coloured with neutral red). The bile salts inhibit the growth of other organisms ; the *Bacillus coli communis* ferments the lactose with acid formation, and turns the neutral red a canary-yellow colour with greenish fluorescence, so that

the colonies of this organism can be readily picked out and used for the preparation of subcultures upon agar slopes, which should then be incubated for eight to twelve hours.

Bacillus of Friedländer.

This organism is especially easy of isolation, as it appears to have the power of inhibiting the growth of almost all other organisms with which it may be admixed. For instance, if equal numbers of *Staphylococcus albus* and bacillus of Friedländer be introduced, each separately, into a tube containing equal volumes of broth, and incubated at 37° C. for twelve hours, equal numbers approximately of each organism will be found in equal volumes of the cultures; but if the two organisms be introduced into one tube of broth in the ratio of 1,000 staphylococci to 1 bacillus of Friedländer, and incubated at 37° C. for twelve hours, the ratio found will be hundreds of thousands of the latter to one of the former.

Whatever the material may be, pus or nasal mucus, all that is necessary, then, is to mix up a little of the material in a tube of broth, incubate for eight hours, and then make agar-plates in the usual manner. Colonies of the bacillus of Friedländer will be found to have attained a considerable size—$\frac{1}{8}$ inch, say, in diameter—after twenty-four hours' incubation, and from one of these agar-tubes may be inseminated.

The Bacillus Septus or Coryzæ Segmentosus.

This organism may also readily be isolated from nasal or pharyngeal mucus by mixing a little of it up in sterile saline or broth, and from this emulsion preparing agar-

plates. Twenty-four hours' incubation at 37° C. will result in the appearance of colonies of considerable size, from which agar-slopes may be inseminated.

Differentiation of this organism from the other members of the diphtheria group is necessary. In microscopical appearance it differs somewhat from all the others. It is a short, rather thick bacillus, with rounded ends, one of which is usually larger than the other. In twenty-four-hour-old cultures it may be so short as to resemble an oval coccus. By the third day a very characteristic appearance is to be seen. The protoplasm of the ends of the bacillus is deeply stained, leaving an unstained band or septum across the middle, hence the name. Involution forms are uncommon and not pronounced, while polar granules are not revealed by Neisser's method of staining.

Gordon considers that the reactions in neutral litmus peptone broth to which 1 per cent. of glucose, lactose, saccharose, and maltose have been respectively added, serves to differentiate this organism completely from the *Bacillus diphtheriæ* on one hand, and from Xerosis and Hoffmann's bacillus on the other. In the case of the *Bacillus septus* there is a tendency to acid formation in all four carbohydrate media, which may not be observed till later than the third day. The *Bacillus diphtheriæ* produces a strongly acid reaction in glucose broth even before three days, while in the cases of Xerosis and Hoffmann's bacillus an alkaline reaction is produced in all four media.

The *Bacillus diphtheriæ* is alone pathogenic to animals.

The Micrococcus Catarrhalis

is best isolated from nasal or pharyngeal mucus by making a succession of stroke cultures on blood-serum or blood-agar plates. The organism is rather like the gonococcus in microscopical appearance, but differs from it in showing considerable variation in size, and also in the fact that the larger-sized organisms tend to retain the stain by Gram's method unless decolorization be very thoroughly carried out. In culture activities it also differs sometimes, growing feebly on gelatine, and also in forming a typical growth in broth. This consists in the formation after two or three days, if undisturbed, of a gelatinous-looking sphere near the bottom of the broth, covered with small spines, giving it a sea-urchin appearance. Subcultures are best made on blood-agar or on nutrose ascitic agar.

It must, however, be noted that other cocci are to be found in nasal and tracheal mucus which closely resemble the *Micrococcus catarrhalis*, and, like it, fail to retain the stain by Gram's method. Differentiation of these catarrhalis-like organisms from the true *Micrococcus catarrhalis* is by no means easy, but the following points are of service :

1. The *Micrococcus catarrhalis* grows in pairs or tetrads, never in chains, like some of the others.

2. It does not produce acid in broth cultures containing glucose, saccharose, maltose, or galactose, whereas some of the others ferment one or more of these sugars.

3. The cocci of the pseudo-catarrhalis group are, as a rule, smaller and more uniform in size and staining reaction.

Morax-Axenfeld Bacillus, or Bacillus Lacunatus.

The isolation of this organism is best carried out in cases of chronic conjunctivitis by taking up some of the thin serous secretion from near the caruncle, and making successive strokes on tubes of blood-serum. After twenty-four or thirty-six hours' incubation characteristic areas of liquefaction of the blood-serum will be evident.

If films be prepared from the bottom of one of these, the typical non-Gram staining diplobacillus will be seen already beginning to involute. A pure colony having been found, tubes of nutrose ascitic agar are now to be inseminated. Inasmuch as this organism begins to involute in from eighteen to twenty-four hours and growth is but feeble (one tube yielding under favourable circumstances but five or six doses), a considerable number of tubes must be employed if any quantity of vaccine be desired.

The Diplococcus Intracellularis (Weichselbaum), or Meningococcus

in cases of cerebro-spinal meningitis is best isolated from the cerebro-spinal fluid obtained by lumbar puncture. A pure growth is obtained by planting this upon agar or blood-serum, where it forms a number of transparent colonies, which run together to form a thin layer. If cerebro-spinal fluid be not obtainable, then isolation must be attempted from the nasal secretion from as high up on the septum and turbinal bones as is possible by means of the platinum loop. Subcultures are best made on blood-serum. In these cases careful differentiation from the *Micrococcus catarrhalis* and pseudo-catarrhalis cocci so commonly present in nasal mucus is necessary.

The points given in the following table are of great service :

TABLE VI.

Diplococcus Intracellularis.	Micrococcus Catarrhalis.
I. Colonies on agar soft and sticky, smooth, or only finely granular, confluent only when crowded.	I. Colonies on agar thicker, more opaque, coarsely granular, readily becoming confluent, and of firm consistency.
II. Cultures in broth are generally turbid.	II. Cultures in broth usually remain clear, with a coarsely granular deposit at the bottom, usually suspended in a mucus-like ball.
III. Produces acid from maltose, and usually from glucose, galactose, and levulose, but not from saccharose.	III. Does not produce acid from any of these carbohydrates.
IV. Does not agglutinate spontaneously in emulsions, but does with the serum of an animal which has been injected with the meningococcus.	IV. Agglutinates spontaneously in emulsions even of considerable dilution.

PREPARATION OF THE EMULSION.

Having thus obtained a pure eighteen- to twenty-four-hour-old growth of the organism on the suitable medium, we now proceed as follows (the tubercle bacillus alone excepted) : The following are the necessary materials : Aluminium or glass rod ; 0·1 per cent. solution of sodium chloride in distilled water, sterilized by boiling ; two small strong Ehrlenmeyer flasks, and three or four small glass

beads, also sterilized ; a centrifuge with 10 c.c. centrifuge tubes ; a sterilizer which can be maintained at any temperature between 55° and 65° C. for one to two hours ; tricresol ; a capillary pipette, with rubber teat ; some sterilized solution of 2 per cent. neutral sodium citrate in distilled water ; four glass slides ; Leishman's stain ; distilled water ; microscope with $\frac{1}{12}$-inch oil-immersion lens and mechanical stage.

If the culture tube do not contain sufficient water of condensation, 4 or 5 drops of the 0·1 per cent. saline solution are now introduced. By means of the aluminium rod the bacterial growth is emulsified as thoroughly as possible.

The two or three tubes are treated in this way, a little more saline added, and the whole transferred to the small flask with two or three glass beads. The tubes are washed out with a few drops of saline, which is added to the first portions. The emulsification of the growth is now completed by agitating the flask for some minutes, the beads helping to break up the colonies present. The emulsion, which should measure about 5 c.c., is now transferred to one of the centrifuge tubes, an equal volume of water being added to the other as counterpoise. After a few minutes' more or less vigorous centrifugalization, according to the size of the organism, the emulsion is poured off from the sediment into the second flask, and is ready for standardization.

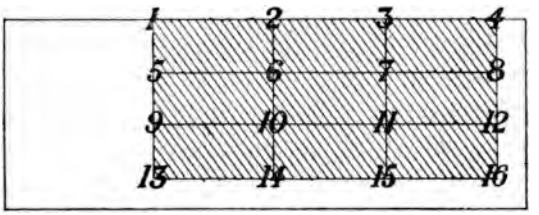
Standardization of the Vaccine.

This is carried out as follows : One end of a few inches of glass-tubing, $\frac{3}{8}$ inch in external diameter, is drawn out into a fine capillary thread, which is then cut off, giving

a total length of 6 to 8 inches. A rubber teat is fitted to the larger extremity, and a mark made upon the capillary thread about ½ inch from the end. This constitutes the unit volume. The emulsion being ready to hand, the finger-tip is pricked on the dorsum, and a drop of blood expressed. By gently compressing the rubber teat, and then slightly releasing the pressure, two or three volumes of the 2 per cent. citrate solution are sucked into the capillary thread; then a small bubble of air, next a volume of blood, then a bubble of air, finally a volume of the emulsion. The whole is then expelled on one of the clean glass-slides, and carefully mixed by alternately sucking it up and expelling it upon the slide. This mixing having been thoroughly carried out, the whole is divided into approximately three parts, which are transferred each to a clean slide, and then carefully and evenly spread by means of the edge of another. In this way uniform smears are obtained. These are allowed to dry in the air, and then stained with Leishman's stain for five minutes. The slides are then flooded with distilled water, which is allowed to remain for fifteen minutes; they are then washed in distilled water till pink in colour, and no more blue escapes into the water, and dried with filter-paper.

They are now ready for counting. By means of a blue grease-pencil the two diameters at right angles are marked upon the ocular of the microscope so that the field is divided into four quadrants. The counting is thereby greatly facilitated, and is carried out as follows: The smear in the slide is mentally divided up into nine equal areas, as in the subjoined figure. A whole field of the microscope is then counted at each of the angles as indicated, so that a total of sixteen fields is counted.

The numbers of red blood-cells seen in each field are set down in one vertical column, the numbers of organisms in another. Each column is then added up, so that the numbers of corpuscles and bacilli respectively in sixteen microscope fields are estimated. This is repeated for the second slide, and the two results added together. These thirty-two fields may be assumed to give a sufficiently accurate count. We will assume that 600 red cells have been counted and 1,500 bacilli. Now, a cubic millimetre of blood contains 5,500,000 red cells, and equal volumes of blood and of emulsion were taken. A cubic millimetre of the emulsion, therefore contains $\frac{5,500,000 \times 1,500}{600}$, or 13,750,000 organisms per cubic millimetre, or 13,750,000,000 per cubic centimetre.



It being desirable to have doses of 125, 250, 500, and 1,000 million bacilli respectively contained in either ½ c.c. or 1 c.c. of fluid, it now becomes necessary to dilute the emulsion. To obtain 1,000 million per c.c. it is obvious that each 1 c.c. of the emulsion has to be made up to 13·75 c.c. with 0·1 sterile salt solution. This is accordingly done, and sufficient tricresol added to made a 0·2 per cent. solution. This is of sufficient strength to inhibit the growth of, or even destroy, any spores of air-organisms which may have gained admittance to the emulsion, and may escape destruction in the subsequent sterilization.

Sterilization of Vaccine.

The flask containing the emulsion is now placed in a sterilizer at 56° to 60° C., and maintained at that temperature for one or one and a half hours, according to the resistance of the organism to heat. The lower the temperature that can be employed with safety, the more potent is the vaccine. It is then allowed to cool, and is ready for the next step.

Tubing the Vaccine.

Materials required: Sufficient sterilized glass serum-bulbs of 1·5 to 2·0 c.c. capacity, in two colours—say white and blue; a standard burette, also sterilized and graduated to $\frac{1}{10}$ c.c.; a hypodermic needle and 2 or 3 inches of thin rubber-tubing, also sterile. To the end of the burette the needle is attached by means of rubber-tubing. The burette being set up vertically, the tap is closed and the emulsion poured in; the tap is then opened till a drop of fluid appears. Into a number of the white bulbs 1 c.c. of emulsion is run, into others $\frac{1}{2}$ c.c. The former will thus contain 1,000 and the latter 500 million organisms. The ends are sealed off by holding in the tip of the flame of a Bunsen burner. A sufficiency of these doses having been made, the remainder of the emulsion is returned in its flask, and 3 volumes of 0·1 saline solution, together with sufficient tricresol to make it up to 0·2 per cent., added. This having been thoroughly shaken up, tubing into the blue bulbs is carried out as before. One c.c. will now contain 250 and $\frac{1}{2}$ c.c. 125 million organisms. We are, therefore, in a position to administer doses of 125 millions and any of its multiples or submultiples.

The bulbs are set aside till next day, when sterilization at 60° C. is again carried out for one hour. These two sterilizations should be quite sufficient to kill the organisms. Should there be any doubt, however, a third sterilization may be carried out on the following day, but is not to be recommended, as the strength of the vaccine may be impaired by too prolonged heating.

The bulbs should now be marked by means of a diamond pencil with the name of the organism and the number contained in each tube. In this way mistakes at any subsequent date will be obviated.

The Various Forms of Tuberculin.

Tuberculin T. (*Koch*, 1890)

is a clear brownish fluid, obtained by filtering through a porcelain filter a glycerine broth culture of tubercle bacilli which has been evaporated on a water-bath to one-tenth its volume.

Tuberculin T.R. (*Koch*).

Young, highly virulent bacilli are dried *in vacuo*, and then comminuted by machinery. The dust thus obtained is heated with distilled water, and the mixture placed in a centrifuge, making 4,000 revolutions per minute. In this way an opalescent fluid (T.O.), possessing analogous properties to the old tuberculin, and a deposit are obtained. The latter is then emulsified with successive quantities of water, and constitutes the new tuberculin, or T.R., which is sold in bottles containing 2, and not, as originally stated, 10, milligrammes of solid bacterial substance per c.c.

The occasional presence of living tubercle bacilli capable of multiplication in the new tuberculin has led to occasional accidents. Wright and Douglas found that heating to 60° C. for one hour sufficed to kill any bacteria and did not impair the tuberculin. After tubing off into appropriate doses, it is, therefore, well to thus sterilize the tuberculin before administration.

Inasmuch as the T.O. thus obtained gives no precipitate with glycerine, while the T.R. does, it is held that the former contains those elements of the bacilli which are soluble in glycerine, and are therefore similar to those contained in the old tuberculin. The T.R., on the other hand, is supposed to be freed from these dangerous constituents. All the immunizing substances of the T.O., according to Koch, are contained in the T.R., and a man immunized with T.R. will not react against a large dose of T.O.

The ordinary T.R. is prepared from bacilli of human origin, and in morphology and cultural reactions conforming to a certain standard.

A similar T.R., known as P.T.R. (Perlsucht T.R.), is prepared from bacilli of bovine origin, which in morphology and cultural reactions differ characteristically from the human type.

Bacillary emulsion (B.E.) is probably the most active of all the tuberculin preparations, and contains 5 milligrammes of bacillary substance per c.c. It may be derived from bacteria either of the human or bovine type, and consists of the comminuted bodies of the bacilli, which are not subjected to any process for removal of toxin, in glycerine emulsion. It therefore stimulates the formation of antitoxic as well as of antibactericidal substances.

Tuberculocidin (Klebs).

Klebs, in 1891, came to the conclusion that the deleterious substances contained in T.O. were of an alkaloidal nature. These he endeavoured to remove, and to the tuberculin thus obtained gave the above name.

Tuberculosetoxin (Maksutow).

Maksutow, in 1897, raised the objection to tuberculin that it was prepared from bacilli grown on artificial culture media, and that the chemical constituents of these media and their disintegration products introduced a complicating factor. A toxin so obtained he held was not necessarily identical with the specific toxin of the bacillus. He therefore made extracts from the tuberculous tissues of diseased guinea-pigs, and from this material obtained a tuberculosetoxin free from bacilli, and capable of producing immunity in animals in about three months.

Tuberculol.

Landman, in 1898, described a preparation in which the bacilli were extracted with normal saline solution, distilled water, and glycerine at progressively increasing temperatures, the first extraction being made at 40° C., the last at 100° C., the different extracts being then added together. To this preparation he gave the name ' tuberculol.'

Bouchard, at the International Congress of Tuberculosis, 1905, also described a new form of tuberculin, which he claimed to be bactericidal *in vitro*, and immunizing and curative in man and animals.

Tulase (*Behring*, 1905)

contains the somatic substance of the tubercle bacillus, which takes up the stain by the Gram and Ziehl-Nielsen methods. The method of preparation is a very complicated one, consisting partly in the treatment of the bacilli with chloral. It may be administered intravenously, subcutaneously, or by the mouth, and is claimed to produce both antituberculous immunity and hypersensibility to Koch's tuberculin. In persons not infected by tubercle immunization by tulase is said to be produced after four months, whereas in those already infected response appears to be more rapid.

Preparation of Combined Vaccines.

In certain conditions, such as pulmonary phthisis, tuberculosis of the bladder and kidneys, and bones and joints, additional gravity is added to the case when to the primary infection secondary ones are added. All are familiar with the comparative ease with which a case of early pulmonary phthisis or tubercular joint disease yields to appropriate treatment, and the difficulty of dealing with such a case when once staphylococci or streptococci have complicated the infection. Occasionally, it is true, great improvement follows the administration of tuberculin alone, but the best results will, I am convinced, be secured by either previously or simultaneously attacking the secondary infection. In these instances it is, as a rule, easy to ascertain the exact nature of this infection. In bladders and kidneys it is usually the *Bacillus coli communis;* in bones and joints, staphylococci or streptococci. Other forms of bacillary

infection there are, however, such as Pyorrhœa Alveolaris, Gleet, and Chronic Tracheal Catarrh, in which it is wellnigh impossible to tell which out of the many different bacteria present are responsible for the condition. The only thing then to do is to employ a 'combined vaccine.' Details of cases and results will be found later. At present attention will be confined to the method of preparing such a vaccine. The first step is to take smears of the discharge. If this be sputum, suitable lumps should be chosen, and washed repeatedly in sterile salt solution before spreading the films. These are then stained with methylene blue and by Gram's method, using neutral red as counterstain. Careful note is made of the organisms present as far as possible, and their relative numbers estimated. Cultures upon suitable media—best upon several, such as upon agar, blood-agar, and blood-serum, and in broth—are also made, and films prepared from these after four, eight, twelve, eighteen, and twenty-four hours' incubation, and stained as before. The identification of the various organisms is thus made more complete, and the medium upon which the relative proportions of the organisms detected in the secretion is best preserved noted, as well as the appropriate time of incubation. Sometimes it will be found that one of the organisms most numerous in the original smears refuses to grow in the presence of the others. There is then nothing for it but to plate out cultures, isolate the various bacteria, make fresh cultures, and prepare the several vaccines separately, and then mix them together. As a rule, however, this is unnecessary. There is nearly always one medium and a certain duration of incubation which will give an emulsion in which the bacteria are preserved in approximately their original proportions.

If one organism be found to outgrow the others, sufficient of it may usually be removed from colonies by means of the platinum loop to re-establish the desired ratio.

It must, however, be admitted that the best and most scientific method is to plate out cultures, isolate the several organisms, omitting any non-pathogenic air organisms which may be present, and from subcultures to prepare the several emulsions, which may be then standardized and mixed in such proportions that the appropriate initial dose of each is secured in ½ c.c. of the mixture.

The usual result of two or three injections at three-weekly intervals of such a vaccine is to produce a most marked reduction in the number and variety of the organisms to be seen in films prepared from the secretion. These may then be dealt with by a fresh vaccine prepared in a similar manner.

Administration of the Vaccine.

The opsonic index having been taken and the suitability of the case for injection determined, the dosage must be decided on. The average initial dose for each organism is given in subsequent pages; it is better to err on the side of too small rather than on that of too large dosage. The best site for injection is in the loose subcutaneous tissue of the side. It may, however, be done in the back or upper arm. Several little points are to be noted; thus, no one can predict how much local reaction may result. In flabby abdominal walls there is usually none. Five or six injections may produce none whatever, and the next quite a considerable amount. A small lump as large as a walnut may be

formed, and the skin reddened. This may be quite painful each time the patient breathes, or coughs, or moves the abdominal wall. This result being possible, it is necessary to provide against it, and the following rules are useful: (1) Do not inject on the side upon which the patient lies; (2) in women do not inject where corsets are likely to press; (3) avoid veins, and so production of a hæmatoma; (4) do not inject so far forwards that any swelling will lie over the edge of the rectus abdominis muscle; (5) remember that if a large fold of skin be picked up and the needle be pushed well in, the inoculum will lie, perhaps, 2 inches from the site of puncture.

A very safe situation is, therefore, on the right abdomen, about ½ inch above the anterior superior spine of the ilium, and about ½ inch internal to it. If a good fold of skin be raised and the puncture made at the spot indicated, the inoculum will lie 1½ to 2 inches internal to the anterior superior spine, and any reaction will cause a minimum of discomfort.

The site, then, having been decided upon, the adjacent skin should be well cleansed with warm soap and water, followed by a little 2 per cent. lysol. The neck of the bulb is scratched with a file and broken off. The inoculum is then sucked up into an ordinary hypodermic syringe, which has been thoroughly sterilized. Any air-bubbles are expelled, and the needle inserted to nearly its full length into the fold of skin and the vaccine expelled. The puncture is then closed with a little collodion. These aseptic precautions may be considered hardly necessary, but infection from the skin or a dirty needle has been known to occur. No care is too great to take to obviate such an unhappy result.

Administration of Vaccines by the Mouth.

Patients, even the best of them, certainly begin to get weary after a time of subcutaneous inoculations, especially at diminishing intervals. Latham[1] has advocated their oral administration. He states that vaccines, if given on an empty stomach, either with normal saline or horse serum (about 10 c.c. in either case), undergo perfect absorption, and produce exactly similar results to when introduced hypodermically. Favourable results were reported in staphylococcal, streptococcal, pneumococcal, and tubercular infections, the ordinary dosages being employed except in the tuberculous cases, where such large doses were employed at such short intervals as certainly are not free from considerable danger if absorption be complete. This method of administration cannot yet be said to have had its utility satisfactorily established; probably it will be found to be of distinct value, but necessarily not so reliable as the subcutaneous method.

[1] Proceedings of the Royal Society of Medicine, 1908, vol. i., No. 6.

CHAPTER V

THE OPSONIC INDEX IN HEALTH AND DISEASE: ITS VALUE IN DIAGNOSIS, PROGNOSIS, AND TREATMENT

The Opsonic Index in Health.

Bulloch determined the indices towards the tubercle bacillus for forty-four medical students and forty hospital nurses, all presumably free from tubercular infection. The results showed a variation from a minimum of 0·8 to a maximum of 1·2 as compared with an index of unity for the serum of himself. The average for the whole eighty-four cases was 0·96. Urwick in twenty cases obtained an average of 1·006, and Lawson and Stewart in twenty-five cases an average of 1·0.

The tuberculo-opsonic index of the average healthy individual should therefore lie between 0·8 and 1·2, approximating as closely as possible to 1·0.

The mean staphylococcal opsonic index of twenty-five healthy adults was found by Bulloch to be 1·0; other observers have obtained a like result, the variation being, as a rule, less than in the case of the tubercle bacillus. Numerous observations with other organisms show that the same holds true in each case; it may therefore be assumed that the opsonic index for any organism of the serum of the average healthy person varies only between narrow limits, the minimum being 0·8 and the maximum 1·2.

The index has also been shown by Urwick to be practically constant from day to day in healthy subjects. He gives the following figures for the tuberculo-opsonic indices of the serum of a healthy individual as compared with his own on various dates :

TABLE VII.

November	1	=	1·1	December	5	=	0·9
,,	8	=	1·0	,,	8	=	0·9
,,	12	=	1·0	,,	13	=	1·0
,,	30	=	1·15	,,	14	=	1·0
				,,	19	=	1·0

Certain factors do, however, produce very slight changes in the index. French, for instance, has found that vigorous exercise, such as a twelve-mile walk undertaken by a healthy person of sedentary habit, will sometimes cause a rise from 1·0 to 1·2 or 1·3 on the following day. Ellett[1] showed that this positive phase was preceded by a negative one. I myself have noticed a diurnal variation very similar to that exhibited by the temperature chart. This is well seen in the following table, the organism employed being the bacillus of Friedländer :

TABLE VIII.

Date.	8 a.m.	9 a.m.	11 a.m.	4 p.m.	12 midnight.	3 a.m.
May 15, 1906 ..	1	1·06	1·14	—	—	—
May 18, 1906 ..	1	1·11	1·20	—	—	—
May 29, 1906 ..	1	1·08	1·08	1·2	1·26	—
June 6, 1906 ..	1	—	1·07	—	1·18	1·0
June 12, 1906 ..	1	1·10	—	—	1·14	—

[1] *British Medical Journal*, July 21, 1907.

From this it would appear that the index is at a maximum between 4 p.m. and midnight, being raised by the active processes of life, a fall to unity rapidly occurring after retirement to bed. Abstinence from food or excessive exercise did not appear to have any immediate effect in the production of a lowered index.

Charteris[1] made observations upon the opsonic index towards staphylococcus and *B. typhosus* of the blood of a man undergoing a fast of fourteen days, during which no food at all was taken. From counts made upon thirty cells he concluded that the index remained practically unaffected by the fast.

The Opsonic Index in Infancy.

Wells and Freeman[2] have made a considerable number of observations upon the opsonic index towards various organisms of the blood of infants from birth up to one year of age. They found practically a normal index at birth, but that it was subject to very great fluctuations from time to time, and concluded :

1. That a low opsonic index is not diagnostic in children under one year old.

2. That a low opsonic index in infants is not inconsistent with health, and that a child may be thriving well with a declining index.

3. That the antibacterial defence in infants cannot depend upon the opsonic content of the serum.

4. That as regards opsonic index the healthy breast-fed infant possesses no apparent advantage over the healthy artificially-fed child.

[1] *Lancet*, September 7, 1907, p. 685.
[2] *Practitioner*, May, 1908, p. 635.

The Opsonic Index in Disease.

1. *In Tubercular Infections.*—Wright, in his earlier experiments upon localized tubercular infections, found a general lowering of the opsonic index below unity. In a series of seventeen cases, exclusive of pulmonary phthisis, he found variations from 0·4 to 0·85, with an average for the seventeen of 0·64.

Bulloch investigated the indices of 150 sufferers from lupus in all stages, from very mild cases to old intractable ones of even forty years' standing. Seventy-five per cent. of the cases had indices below 0·8, while the average for the 150 cases was 0·75, distributed as follows :

TABLE IX.

Opsonic Index.	Number of Cases.	Percentage.
Between 0·2 and 0·3	3	2·0
,, 0·3 ,, 0·4	3	2·0
,, 0·4 ,, 0·5	21	14·0
,, 0·5 ,, 0·6	29	19·6
,, 0·6 ,, 0·7	33	22·0
,, 0.7 ,, 0·8	22	14·8
,, 0·8 ,, 0·9	18	12·0
,, 0·9 ,, 1·0	7	4·6
,, 1·0 ,, 1·4	14	9·3

In chronic cases of surgical tuberculosis, such as of the joints, kidneys, bladder, or glands, it appears to be generally low, an average of 0·6 being obtained by Bulloch in eleven cases, and of 0·8 in nine cases by French.

Lawson and Stewart made between 2,000 and 3,000 observations upon cases of apyrexial phthisis, and found the index to be always below 1·0, varying from 0·5 to 1·0.

Urwick examined thirty-three cases of pulmonary

tuberculosis in all stages. In twenty-five he found an index above 1·0, even as high as 2·6; in seven an index below 1·0; and in one case the index was 1·0.

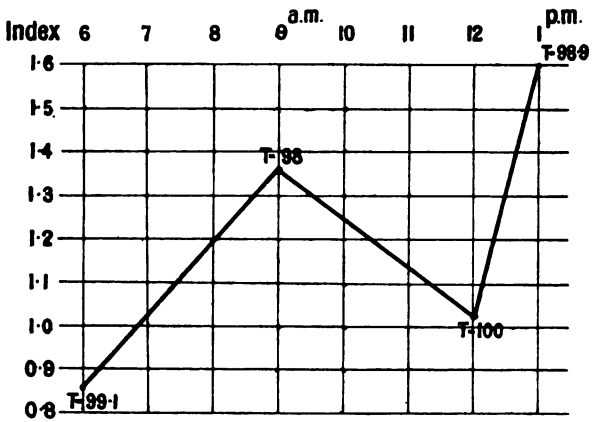
Effect of Exercise upon Tuberculo-Opsonic Index in Cases of Phthisis.

These variable results were explained by Meakin and Wheeler,[1] who studied the index at various times of the day in tubercular patients who were undergoing sanatorium treatment, some of whom were taking walking exercise and others not; specimens of blood were taken at 6 a.m., 9 a.m., noon, and 1 p.m. If the patient was capable of taking exercise, this was done between 9 a.m. and noon; between noon and 1 p.m. rest was taken in a long chair.

The results of some of their observations—five upon patients taking exercise, and three not—are shown in the adjoined charts:

MEAKIN AND WHEELER. WALKING CASES.

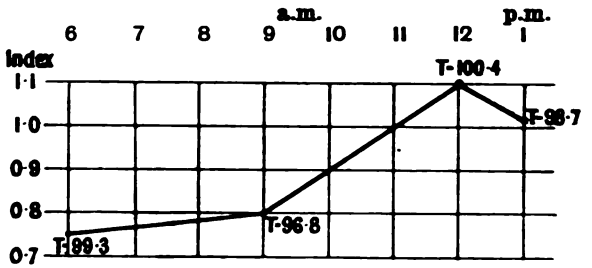
CHART II.



Case No. 1. Walking. September 18.

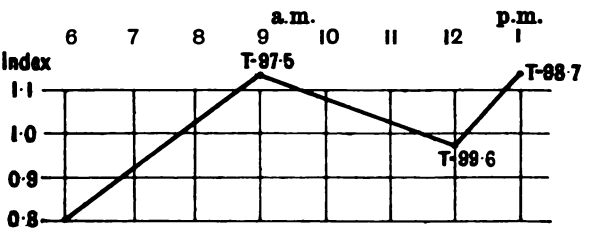
[1] *British Medical Journal*, November 25, 1905, p. 1396.

CHART III.



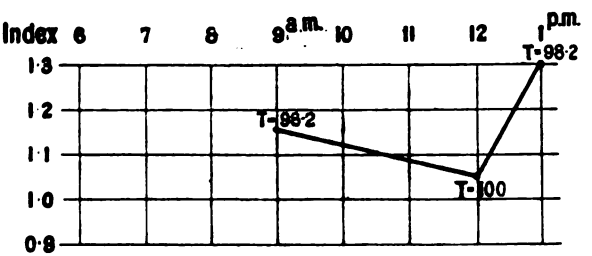
Case No. 2. C. T. Walking. September 27.

CHART IV.



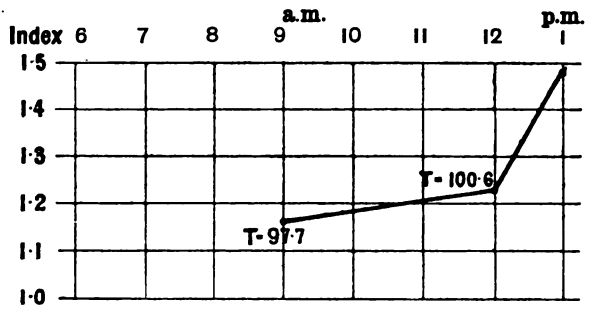
Case No. 3. W. L. Walking. September 28, 29.

CHART V.



Case No. 4. R. C. Walking. October 11.

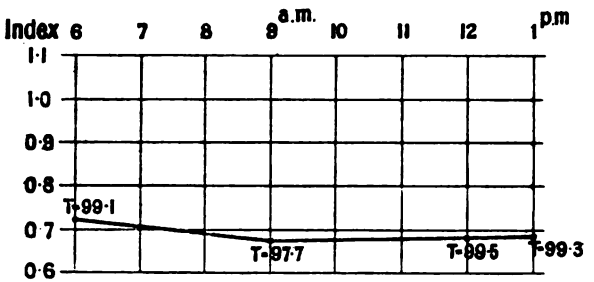
CHART VI.



Case No. 5. H. M. Walking. September 16.

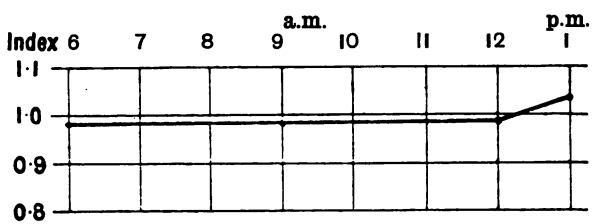
MEAKIN AND WHEELER. RESTING CASES.

CHART VII.



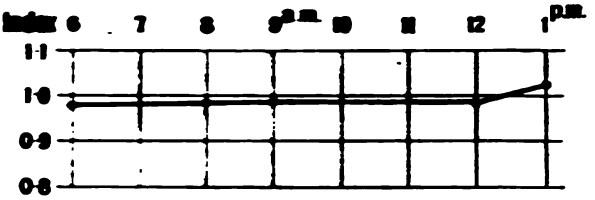
Case No. 5. H. M. Resting. October 1.

CHART VIII.



Case No. 6. H. B. Resting. September 18.

CHART IX.



Case No. 7. D. H. Resting. October 4.

It will be observed that in all the walking cases except one a much higher index was recorded at 1 p.m. than at 9 a.m., and that this rise bears no obvious relation to rise of temperature, whereas in resting cases the index is practically constant, and either at or below unity throughout the day. This is taken to indicate that in walking cases there occurs a process of auto-inoculation by absorption of extremely minute doses of tubercular toxin by the very vascular lung tissue. How minute the dose is, the shortness of the negative phase (two or three hours) clearly indicates. The process thus exactly resembles the succession of negative and positive phases which, as we shall see, is induced by a series of tuberculin injections.

Confirmation of this view is afforded by the like results which we shall see later are produced by surgical manipulation of a tubercular joint. It would thus appear to be generally true that in pulmonary phthisis—

The index is above 1 in slight early cases.
The index is variable in acute cases.
The index is below 1 in chronic cases.

In acute cases there may be either a constant high index, where the body is making every effort to cope with the invaders and the conditions are favourable; or fluctuating, where auto-inoculation is occurring—not, as

Wright suggests, with too large or badly interspaced doses, but with infinitesimally small ones, so that negative and positive phases are alike of short duration, though full amplitude; or, finally, it may be constantly below unity, if such auto-inoculations be prevented.

In tubercular infections of the eyeball, uncomplicated by tuberculosis elsewhere, the index is usually high. Thus, a case of tubercular iritis had an index of 1·3, a case of keratitis an index of 1·5. A third case, in which tubercular keratitis and iritis were complicated by tubercular cervical and mesenteric glands and by peritonitis, had, on the other hand, an index of 0·4. As will be mentioned later, all eye infections, whether acute or chronic, are usually attended by high opsonic index. The explanation of this is, I think, fairly obvious. The circulation of the eyeball is so poor and the infection so localized that the very minute doses of toxin absorbed act exactly like repeated injections of infinitesimally small doses of tuberculin — so small that the protective mechanism of the body is not exhausted. That chronic cases do not get well with this high index is, again, probably due to the poor circulation, and consequently to the small amount of opsonin brought to the part.

Eyre has observed that broken-down phlyctenules may be starting-points for tuberculosis of the conjunctiva, while Wright, in his earlier experiments, noticed that occasionally phlyctenules developed in patients undergoing inoculations with tuberculin. Nias and Paton[1] accordingly investigated the tuberculo-opsonic index in a series of twenty cases of early phlyctenular conjunctivitis, employing five cases of other forms of conjunctivitis as controls. They found striking variations from

[1] Trans. Ophth. Soc., November 9, 1907.

the normal in the indices of the cases of phlyctenular conjunctivitis, and practically normal indices in the other forms. The author has obtained similar results, but it must not be lost sight of that phlyctenules usually make their appearances in definitely tubercular subjects, and that the disturbance of the index is probably in the major part due to infected glands, lungs, bones, or joints.

In Other Infections.

2. (*a*) *In Acute Cases.*—What has been said of pulmonary phthisis holds equally for other organisms. When the body is making a satisfactory immunizing response, the index may be maintained at a constant high level and above normal; when auto-inoculations are occurring, the index will be fluctuating; while in acute cases, where the immunizing machinery is in default, the index will be low.

(*b*) *In Chronic Cases.*—Here the index is almost uniformly low. Should, however, an auto-inoculation occur, then an immunizing response may be elicited, and the index be raised above normal.

Da Costa[1] studied the opsonic index towards *Staphylococcus aureus* in twenty-two cases of diabetes. Sixteen of these were cases of true diabetes mellitus, and all showed subnormal indices, varying between 0·34 and 0·72, the average being 0·62. The liability of diabetes to boils and carbuncles is thus explained. Four cases of diabetes insipidus had indices between 0·8 and 0·9, and two of transient glycosuria had indices of 0·8 and 0·9.

C. J. Shaw[2] determined the indices in fifteen insane

[1] *American Journal of Medical Science*, July, 1907, p. 57.

[2] *Journal of Mental Science*, January, 1908, p. 57.

patients towards the tubercle bacillus, *Bacillus coli communis*, *Staphylococcus*, and *M. rheumaticus*. The number of cells observed was never more than fifty, and his figures do not appear very convincing, but he concluded that in the insane the index to the above organisms is generally lower than in the sane, and the amount of variation greater. From consideration of the indices he deduced that the acutely mentally affected are more liable to organismal infection than more chronic cases, but that the latter have less resisting power than the sane.

The Effect of Menstruation upon the Index in Infected Cases.[1]

An important point to remember in connection with a female infected by any organism is that menstruation produces a very marked lowering of the index to that organism—an effect which may begin a day or two before the period and persist for a day or two after ; the fall and rise, once initiated, move with great rapidity. It is, however, stated that in non-infected females there is a general depression of the opsonic index to all organisms ; this statement needs confirmation.

The Opsonic Index as an Aid to Diagnosis.

1. *In Cases of Supposed Tuberculosis.*—It has been mentioned that the index to the tubercle bacillus of the sera of healthy subjects varies between 0·8 and 1·2. The important question now presents itself as to how we are to regard an index which does not lie within these limits. Does it mean that infection has already taken place, or merely that the person is predisposed

[1] French, *Practitioner*, July, 1906.

to it ? That a low index always means the former of these alternatives is certainly not the case, as is shown by the following instance : Dr. Eyre, while directing the work of the Commission on Mediterranean Fever in Malta, contracted the disease severely. After a short interval it was found that his index to the tubercle bacillus, which was known to be normal before his departure from England, was below 0·4. It remained at this low level for several weeks, and only slowly returned to normal. There never was any evidence soever of his having been infected by tubercle. A similar effect was also noticed in the case of Dr. C. Pryce Jones after contracting Malta Fever.

It is probable that a low index precedes infection, and is due either to an acquired or hereditary inability to elaborate the chemical protective substances of the body. It is possible that a fall in these bacteriotropic substances, which is local and not general, will suffice to determine infection in certain cases. As we have seen, a low index is the rule in chronic localized infection; and in any case of supposed tuberculosis where a low index is found, especially in the instance of a patient not coming from tubercular stock, and where clinical appearances are compatible with such a diagnosis, tuberculosis is highly probable. It must not be forgotten that a depression of index may persist for a long time after an infection is supposed to have been cured. Thus, in fourteen picked cases of sanatorium ' cures ' of phthisis in its early stages, Bulloch[1] found indices varying between 0·4 and 0·86. Lawson and Stewart[2] examined the indices of twenty-five such cases. In five of these it was found to lie between 1·1 and 0·9; in the other twenty it was 0·8 or under.

[1] *Lancet*, December 2, 1905, p. 1603.
[2] *Ibid.*, December 9, 1905, p. 1683.

Consideration of these results, taken in conjunction with the extreme frequency with which indications of healed tuberculosis, either of bronchial glands or lungs, are found in autopsies upon those never recognized as tubercular subjects while alive, tends strongly to support West's view that all cases in which low indices, not explicable by such considerations as were noted in Chapter I., are found are instances either of cured or active tuberculosis. On the other hand, an abnormally high index—1·3 or over—is probably almost always asign of active infection.

Reliance should not, however, be placed upon a single determination of the index ; two at least are always advisable. Should these not agree, then a series should be done before a definite conclusion is arrived at. Continual variations certainly indicate active infection and a succession of auto-inoculations. *Per contra*, the non-occurrence of a high or fluctuating index in patients acutely ill is very strong evidence against a diagnosis of tuberculosis, and lends support to such alternative diagnoses as malignant disease of the lung, chronic bronchitis and emphysema, bronchiectasis, general debility, or gonorrhœal arthritis.

An abnormal index will assist in discriminating such conditions as—

Tuberculous kidney from malignant kidney or renal calculus.
Addison's disease from pernicious anæmia.
Tubercular peritonitis from malignant peritonitis.
,, laryngitis from malignant laryngitis.
,, pleurisy from malignant and other forms of pleurisy.
,, joints from syphilitic and gonorrhœal joints.
,, adenitis from Hodgkin's disease.
,, endocarditis from fungating and other forms of endocarditis.
,, keratitis and iritis from syphilitic and rheumatic.

Tubercular epididymorchitis from syphilitic, adenomatous, or malignant forms.
,, cystitis from that due to calculi, tumours, enlarged prostate, etc.
,, salpingitis from gonorrhœal.
,, ovary from malignant or cystic.
,, endometritis from malignant, etc.
Lupus from syphilis or rodent ulcer.

2. *In Other Cases.*—Opsonic index determinations have been shown in numerous instances to be of the utmost value in the investigation of infections of doubtful nature. Thus, Houston and Rankin[1] demonstrated their great value in the diagnosis of suspected cases of cerebro-spinal meningitis, in which the index is always high, and in the differentiation of the true form of this disease from posterior basic meningitis.

In three cases of suspected non-specific urethritis during the past year, the author has been enabled to make a definite diagnosis, and to exclude the gonococcus—rightly, as subsequent events proved. The differentiation of an acutely rheumatic or gonococcal joint from one infected by other pyogenic cocci is greatly facilitated, and the correct diagnosis of the infecting agent in septicæmic cases where no organisms can be isolated from the blood rendered possible.

A study of the opsonic index in typhoid fever may well prove especially productive of valuable results, and enable a diagnosis to be established earlier than is now possible by any other means. The careful study of Wright and his co-workers[2] upon the artificial production of auto-inoculations has rendered available a method of extreme value for determining whether an infective focus has completely healed or merely lies dormant.

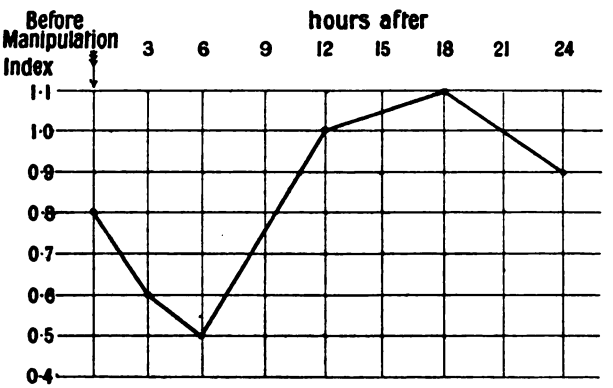
[1] *British Medical Journal*, November 16, 1907.
[2] *Lancet*, vol. ii., 1907, p. 1217.

Special Methods of employing the Opsonic Index in Diagnosis.

The first method depends upon the artificial production of an auto-inoculation, and is especially applicable to tuberculosis and other diseases of joints. The index is taken ; passive movement of the joint is then performed by the surgeon, and fresh determinations of the index done after three, six, twelve, and twenty-four hours. Should infection not be present, minimal variations in the index will be found ; but should it be present, the production of definite negative and positive phases will be evidenced. The negative phase may be fully produced within three hours or may be absent.

The adjoined chart shows the effect produced in a case of doubtful tuberculosis of the hip in a child six years old :

CHART X.



Ample confirmation of the diagnosis was thus secured.

The second method is of wider applicability. A small dose of T.R. (0·00002 to 0·00004 c.c.) is given, and the index estimated daily.

In healthy subjects the negative phase, if present at all, is of very slight amplitude and short duration, lasting, as a rule, for only a few hours. The positive phase resembles the negative, and the limit of fall and rise in the index rarely exceeds 0·2 or 0·3. Lawson and Stewart[1] found no negative phase, but a rise in one instance from 1·0 to 2·1 within a few hours. In infection, on the contrary, a much more pronounced fall and rise are, as a rule, obtained ; the negative phase may last for days, or even a fortnight, and the crest of the positive phase be not attained for one to three weeks. Inasmuch as occasionally no negative phase is produced in cases undoubtedly tubercular, failure to obtain a negative phase does not entirely put the diagnosis of tubercle out of consideration. A third method is the employment of the original tuberculin in doses insufficient to produce the acute disturbances originally obtained. Dodds[2] reported the effect of injections of T.O. in doses containing 1 milligramme of solid substance upon the opsonic index in five doubtful cases of phthisis, and in one certain case exhibiting bacilli in the sputum. In this latter instance the index before injection was 0·7 ; twelve hours after injection of 0·5 milligramme of T.O. the index = 1·1 ; upon the fifth day it had fallen to 0·9. Of the other five cases, in four the index was normal, and remained so after injection of 1 milligramme of T.O. Of these, three were cases of old pneumococcal pleurisy, with chronic cough for months ; the fourth had a chronic cough. In the fifth case the index fell from 1·0 to 0·7, and rose next day to 1·4. He had a phthisical family history, and had had pleurisy six

[1] Edin. Med.-Chir. Trans., November 1, 1905. Proc. Royal Med.-Chir. Soc., November 28, 1905.

[2] *British Medical Journal*, July 7, 1906, p. 22.

years previously, with persistent subsequent cough ; his sputum was streaked with blood, and occasional night sweats were present. In this case the diagnosis of phthisis was held to be confirmed.

A fourth method depends upon the fact, already noted, that in females infected by an organism the onset of menstruation initiates a very marked fall in the index towards that organism ; the cessation as pronounced a rise. If, therefore, a female be suspected of tuberculosis, determinations of the index a couple of days before the onset, towards the end of the period, and two or three days after should reveal marked negative and positive phases.

In two cases of severe recurrent episcleritis which is by some eye pathologists considered to be of tubercular origin, I utilized this method. In the first the tuberculo-opsonic index before menstruation was 0·96, and during menstruation 0·93 ; tuberculin injections were therefore not advised.

In the second case it was 1·26 before menstruation, and 1·28 during the period. No other clinical evidence of tubercle could be found, and, as before, despite the somewhat high index, tuberculin injections were held to offer slight chance of improvement. As, however, the patient came from tubercular stock, and wished to avail herself of every chance, four injections were given at three weekly intervals, but without producing the slightest improvement.

A fifth method, whereby the presence of a suspected infection can be established, has been devised by Peel Ritchie,[1] and should prove especially useful in cases where an index upon the border-line of the normal—say 0·8—has been obtained by the usual method. If the serum of an infected individual be compared with a

[1] *Lancet*, November 16, 1907, p. 1419.

normal serum, not only undiluted, but also when diluted with five volumes of normal saline, it will be found that the index is lower for the diluted than for the undiluted sample. But if the two sera be treated with a thick suspension of a bacterium other than that with which the individual is infected, and the index towards the infecting organism be determined for the diluted and undiluted sera, a different result is obtained ; the serum of the infected individual will now show a much higher relative value than before. Thus the serum of a certain tuberculous person was compared with that of a healthy one and found to have an index of 0·73 ; both sera were then diluted five times with normal saline, and the index found to be 0·53. The phagocytic power towards the tubercle bacillus was then redetermined for the diluted sera, a considerable amount of a culture of *Bacillus coli communis* being also added to the phagocytic mixture. The tuberculo-opsonic index of the diluted serum of the infected individual was now found to be 1·31.

This depends upon the fact, as we have seen, that in the blood of an infected individual opsonin specific against the infecting organism is elaborated, and it is the amount of specific opsonin which is alone estimated by this latter procedure.

For tubercle estimations Ritchie advises the addition of *Bacillus coli communis* to absorb the non-specific opsonin, and for other estimations absorption with the aid of tubercle bacilli. The relative rise is rarely less than 0·2, and is often very striking. Ritchie employed this method in 150 cases of varied infections with striking success. Failure occurred in only eleven cases, which were all tubercular ; the explanation of this will be given later (see p. 104).

THE OPSONIC INDEX AS AN AID TO PROGNOSIS.

1. *In Pulmonary Phthisis.*—It is beyond question that the cases of pulmonary phthisis which do worst are the pyrexial ones, and, as we have seen, these exhibit violent fluctuations in the index. Rest in bed steadies the temperature and opsonic index alike. The level taken up by the latter varies considerably in different cases, and sufficient evidence is not yet forthcoming to enable a definite opinion to be given as to the import of a steady high or low index.

Taking into consideration the facts that chronicity is always accompanied by a low index, and that the aim of therapeutic injections is to raise the index to or above unity, it would appear rational to assume that those cases will do best which settle down to a steady index of 1 or over, while those that settle down to an index below 1 will go on to chronicity. Meakin and Wheeler support this view. They find that the case with an index much below 1 is the case that becomes chronic, that recovers to a certain extent, but can only maintain that degree of recovery while living under sanatorium treatment; that the case, on the other hand, which during treatment shows a steady index of 1 or over is the one which makes a complete recovery if favourable conditions are maintained for a sufficient time. They lay especial stress on the statement that it is only to patients actually undergoing sanatorium treatment that this opinion applies.

Lawson and Stewart[1] took the indices of twenty-five cases of sanatorium 'cures.' In five of these it was found to be between 1·1 and 0·9; in the other twenty it was 0·8 or under.

[1] *Lancet*, December 9, 1905, p. 1683.

In thirty other similar cases fourteen had indices between 0·5 and 0·9, and of these thirty cases twenty-nine had been carrying on their usual occupations, in most instances in towns, for periods ranging from six months to four and a half years, and enjoying perfect health.

As to the liability of cases with low indices to relapse, nothing definite is at present known, but authorities agree upon the distinct advisability of artificially raising to unity or over the indices in all such cases. The cases which seem to profit most when tuberculin injections are added to the other therapeutic measures adopted at sanatoria, appear to be those with initially low indices, although improvement is also noticeable in those with indices above unity.

2. *In Other Tubercular Affections—Lupus.*—Bulloch's experience is that the cases which do best with Finsen light are those with indices either beyond or within the normal limits; those with indices below 0·8 do worst, whereas, *per contra*, those cases which profit most from tuberculin injections are those of the latter class. Wright finds that in those varieties of lupus where the infected skin is dry and scaly, so-called lupus psoriasis, tuberculin is of little avail; while in suppurating lupus, where mixed infection by the *Staphylococcus albus* is present, good results can often only be achieved by a simultaneous attack upon the secondary infection.

As regards other tubercular affections, such as those of glands, peritoneum, joints, kidneys, and bladder, no definite rules can be laid down beyond the general statement that if tuberculin injections are not to be given, the cases that have a steadily high index do best, while those with fluctuating indices do badly, and those with subnormal indices

show little tendency to recover. These last show the relatively greatest improvement under a course of tuberculin, but as experience increases it becomes more and more difficult to draw the line between suitable and unsuitable cases for such treatment, for some cases which have seemed the most hopeless have yet done well. In four cases of tubercular peritonitis which relapsed, White found subnormal indices; in one which recovered, an index above normal.

3. *In Other Infections.*—No general rule whatever can here be laid down. A low index denotes lack of immunizing response, and therefore chronicity or complete ultimate failure of the protective mechanism; a high index obviously denotes an attempt at adequate immunizing response. The attempt may succeed, or it may fail, either because it is inadequate or because the other protective mechanism breaks down. That death is often preceded by an abnormally high index has mystified many; in reality there is no difficulty in understanding it at all. It is then a last supreme effort on the part of the body to overcome the infection; into what may be its most powerful line of defence it hurls up all its reserve supports, but in vain. The other protective mechanisms do not suffice; the vanguard is strong enough, but the flanks are weak and the rear unguarded. For instance, in a case of septicæmia the opsonin may be adequate—perhaps more than adequate—but what avail is this if the myocardium has been hopelessly weakened by toxin? Of what use, again, is an index of 15 in cerebro-spinal meningitis, when the cerebro-spinal fluid has an index of zero and all the cerebral centres are overloaded with toxin? Yet the body will keep up the fight to the bitter end, and in a last effort perhaps raise the index to 30.

The Value of the Opsonic Index as a Guide in Therapeutical Immunization.

It is with considerable diffidence that I enter upon the task of discussing this very vexed and much-debated subject; the doubts cast by insufficiently skilled observers and others upon the accuracy of the present methods of determining the opsonic index, and upon its value as a measure of the immunizing response of the human organism to inoculation, have sunk so deeply that there are those who say, 'Away with the opsonic index; let us immunize without it!' There are those, again, who hold views diametrically opposed to these, and, proceeding with the utmost caution, would never give an inoculation without prior determination of the index; and there are those, again, who reserve this observation for such occasions as when they find themselves in difficulties. My own procedure with patients is as follows: No matter what the infection may be—a simple staphyloma, a case of pulmonary phthisis, or a systemic infection—I always explain that in the present state of knowledge I feel that the best results are only to be secured by systematic observation of the opsonic index. Should financial considerations intervene, then two alternatives are offered: the occasional determination of the index at such times as clinical symptoms point to alternation of dosage, or of frequency of administration, or the conduct of the case with the aid of past experience and clinical observation. In both these cases I cast all responsibility for possible failure upon the patient; in other words, I do not think that inability on their part to pay for a series of difficult laboratory estimations should deprive them of the benefits likely to accrue from a course of inoculations,

but they cannot expect the most favourable or speedy issue.

The difficulties liable to be encountered by those who would undertake the conduct of therapeutical immunization without the guidance of the opsonic index are so especially clearly outlined by Sir A. E. Wright, in his illuminating article in the *Practitioner* for May, 1908, that I cannot do better than make the following extract:

'The suggestion has been proffered by many that the clinical symptoms of the patient will furnish the immunizator with a guide by which he may regulate his procedure, but to this suggestion many objections may be taken. For instance—

'1. Even in the case of localized infections, where objective and other signs are freely presented, many difficulties of interpretation may be present. Thus, in lupus secondarily infected by streptococci incidental exacerbations of the secondary infection may completely mask amelioration in the tubercular infection; and this is equally true of other mixed infections. Again, variations in the size of tubercular glands, and perhaps changes in the amount of effusion into tubercular joints, may occur, independently of any progress or regress of the infection, directly as the result of changes in the coagulability or viscidity of the blood.

'2. The clinical symptoms, even when conveying accurate information with respect to the conditions obtaining in the focus of infection, may suggest quite a wrong picture of the conditions obtaining in the circulating blood.

'3. The fact that the patient's general condition remains undisturbed does not warrant us in assuming that the

antibacterial potency of the blood is not undergoing momentous fluctuations under the influence of spontaneous auto-inoculations such as the immunizator should take into account in regulating his dosage and in interspacing his inoculations.

'4. Many conditions there are of a strictly localized infection, where the conditions are unfavourable to the observation of changes in the condition of the focus of infection, such as the majority of cases of tubercular adenitis, arthritis, lupus, and phthisis. Of course the clinical symptoms would ultimately inform as to the results of the course of vaccine therapy, but this information arrives too tardily to be of service. The necessity is obvious of determining, from time to time, what the scheme of dosage is achieving for good or ill.

'5. In acute febrile conditions, while it is true that the rule is to find an inverse relation of temperature to antibacterial potency, it is certainly not the invariable rule. It is notorious that excessive intoxication may condition a fall in temperature, and it is conceivable that a rise in temperature may sometimes be associated with efficient immunizing response.

'6. Finally, there are cases where all local and general symptoms are in abeyance, or have returned to the condition which prevailed previous to inoculation. Here we are face to face with the difficulty as to whether the patient is now immune, whether the infection has been eradicated or still persists.'

With these important considerations before us, I think that even the most prejudiced will admit that therapeutic immunization is a course not lightly to be embarked upon, and that in the present state of our

knowledge the greatest caution is to be used if the pilotage of the opsonic index be dispensed with, especially in cases where the effects of a mistake will be of serious import to the patient. This question will, incidentally, be further referred to in the chapters dealing with the specific infections.

CHAPTER VI

INFECTIONS BY THE TUBERCLE BACILLUS

I. ÆTIOLOGY OF TUBERCULOSIS.

IT is a most unfortunate thing that in all that appertains to the tubercle bacillus there is still so much that is uncertain. Out of the chaos a gleam of light appears, but a vast amount of work remains yet to be done before the immunizator can approach a case of tuberculosis with any great degree of confidence.

Even upon the question of ætiology finality has not yet been reached. Koch and Cornet still uphold that the disease is spread by direct infection from individual to individual, and that the human and bovine types of bacilli are quite distinct. A severe blow has been dealt to this theory by the experiments of Vansteenberghe and of Whitla and Symmers, which bear out Behring's view that direct infection is not proven, and that nearly all tuberculosis is the result of infection by means of contaminated milk. Vansteenberghe and Grysez, by means of most careful feeding experiments upon animals through an œsophageal tube with tubercle bacilli, showed that the organisms were absorbed by the intact intestinal mucosa, and produced extensive tuberculous deposits in the mesenteric and other glands, lungs and other viscera; within even ten days the whole lymphatic system became infected, and in fifty to sixty days the cervical glands

were deeply infected. Whitla and Symmers fed animals through a tube with china ink and carbon particles, and also injected them both intravenously and intraperitoneally with the same preparations. In each instance they were able to demonstrate that the solid particles were very rapidly carried to the lung. Vansteenberghe has pointed out a very remarkable difference between young and old animals in the permeability of the lymphatic glands. In the case of the former the bacteria are rapidly filtered off by the glandular tissue, which accordingly becomes deeply infiltrated, while the lungs may remain free ; whereas in old animals the glands have not this power, and great numbers of the bacteria pass through them, and reach the lung via thoracic duct and blood-stream. Flugge, Ribbert, and Schrotter hold that the droplets of sputum laden with tubercle bacilli coughed up by an infected individual are an important source of infection ; and Flugge adduces experiments to show that pulmonary phthisis can be induced in a number of animals by inhalation, and that the number of bacilli required to produce infection by ingestion is millions of times greater than that required to produce infection by inhalation, and consideration of cases of primary laryngeal tuberculosis leads to the conclusion that such cases can only have been induced by inhalation.

Pottenger says : ' The presumption is quite strong that phthisis is primarily a glandular disease, the bacilli gaining entrance through the mucous membrane, and being either destroyed or deposited in the lymphatic glands. Infection may take place in childhood, but death may not occur till adolescence or even old age. The bacilli may remain in the lung during an entire lifetime and produce no recognizable symptoms ; they may re-

main and produce symptoms at times, and yet never cause advanced tuberculosis, or, being there, they may cause an active disease at any time.' He points out that the floors of rooms occupied by phthisis patients are very apt to be contaminated, and the grave consequent risk to a child crawling about on the floor of constantly putting his infected hands into his mouth. Ravenel has pointed out that the chances of infection via the tonsil either from inhaled bacilli of human origin or from the bovine bacilli in infected milk also have to be considered, especially in view of Grober's demonstration of a direct route to the pleura and lungs via the cervical lymph-glands.

That tubercle bacilli can pass through the intact mucous membrane of the intestinal tract must now be regarded as proven, and MacConkey and MacFadyen have found virulent tubercle bacilli present, usually in the mesenteric glands, of about 25 per cent. of children who have died from non-tuberculous causes. Against this theory that the common route of infection is via the intestine is to be set the fact that, in Siam and Japan, where all children are breast-fed, and cow's milk is not drunk, pulmonary phthisis is yet rampant. A similar state of affairs is found in Egypt, Malaya, India, and Persia.

By the upholders of this theory of intestinal infection by means of cow's milk a very difficult question remains to be answered. The minute and careful examinations of Spengler in Germany and of Pottenger in America, and confirmed by numerous other observers, establishes it as a fact that by far the greater proportion of lung cases are infected by the human type of bacillus. How, then, can these cases have been set up by an infection of bovine origin, unless it be that the latter type becomes

converted into the former by long residence in the human body ?

I would suggest that all extremists are in error, and that there are numerous modes of entrance of the bacilli into the body ; that they may gain access in contaminated milk and butter through the intact mucous membrane of the intestinal tract, lodge in the mesenteric and bronchial glands, and perhaps find their way into the lung tissue through the blood-stream ; that, again, human bacilli may similarly be swallowed in dust and sputum and follow the same course ; that either bovine in milk or human in sputum may be caught up by the tonsil and lodge in the cervical glands ; or yet, again, that inhalation may be responsible for infection via the respiratory tract. This question of ætiology only affects the immunizator in so far as it sheds light upon the variety of the bacillus at work in any given case.

II. Methods of Diagnosis of Tuberculous Infection.

(*A*) *By Clinical Signs.*—These will be found fully described in any such work as Pottenger's ' Pulmonary Tuberculosis.'

(*B*) *Special Methods not Dependent upon Determination of the Index.*

1. *The Old Tuberculin Test.*—If a healthy individual receive an injection even so large as 0·01 c.c. of old tuberculin (Koch), no symptoms beyond slight local tenderness will be exhibited. The case is very different with a person affiicted with tuberculosis, especially if in an early stage. If the dose of tuberculin be extremely small, no effect may be noted ; if a larger, a local hyperæmia

of the infected area; if still larger, a congestion; while if larger still, a constitutional disturbance of varying degrees of severity will result. If the infected areas be visible, as in the larynx or pharynx, the hyperæmia and congestion can be readily detected. In the lung there is an increase in the symptoms confined to the area of infection; the auscultatory signs are magnified, and resemble a catarrhal condition of greater degree. Fine râles may appear where none were to be found previously, or their number may increase. Careful charting of the signs before and during the reaction are therefore necessary.

It is possible to have this local reaction without any general one. If the latter be present, a few hours after the administration of a small dose of tuberculin the patient begins to feel a little nervous or tired, and perhaps has a heavy feeling about the limbs. With this there may be a slight rise of temperature of a fraction of a degree or a slightly accelerated pulse. With a larger dose the tired feeling and heaviness of the limbs becomes a true ache, which extends to the back and head, and the feeling is that of an oncoming cold. With this the temperature usually rises one or two degrees, and the patient may develop a cough where none was present before. If the dose be still larger, the patient may have a rigor, and nausea and vomiting occur.

The more experienced the physician, the less the amount of general reaction that he requires to establish a diagnosis, and an endeavour is made so to adjust the dose that a rise, at all events, of not more than 1° F. shall occur in the temperature. If this be already above 100° F., the use of the test is contra-indicated—at all events, until rest and other appropriate means have reduced the temperature to the region of the normal.

Inasmuch as the reaction usually shows itself in from eight to twenty hours, the dose of tuberculin is best given at eight or nine o'clock at night, the temperature being then taken at six o'clock next morning and at two-hourly intervals. Examination of the chest for the local reaction should begin at the same time, and be repeated at three to four hourly intervals until the presence or absence of local reaction is established. For the purpose of the test Koch's old tuberculin is usually employed. Some people being very sensitive to it, it is best to begin with a dose of only 0·0001 c.c., to which only very exceptionally is any response made. Should no reaction occur, the dose is increased; 0·001, 0·003, 0·005, 0·007, 0·01 c.c. being used in succession at one or two daily intervals until a positive result is secured, as is usually the case with the second or third of these doses in tuberculous cases. A negative result with the last of these doses is considered to be final. It must be remembered that some cases of advanced phthisis will not respond to the test, while it is also possible that cases infected by the bovine bacillus may not react to tuberculin of human origin (as in eleven cases of Peel Ritchie, referred to on p. 88). It has also been stated that certain cases of syphilis have given a positive reaction, but against this it must be borne in mind that sufficient proof that these cases were not also infected somewhere by the tubercle bacillus has not been always forthcoming.

Contra-indications to use of the test are: (1) If temperature rises above 98·6° in the axilla, or 99° F. in the mouth; (2) if definite signs of tuberculosis be present, if tubercle bacilli be present in the sputum, or if there has been a recent attack of hæmoptysis; (3) if there be grave renal or cardiac trouble; (4) if patient be subject to epileptic fits.

2. *Von Pirquet's Cutaneous Reaction.*[1]—Von Pirquet employed a solution consisting of Koch's old tuberculin 1 part, 5 per cent. carbolic acid 1 part, normal salt solution 2 parts, and showed that by its means a reaction could be obtained in persons infected by the tubercle bacillus, which is but rarely obtainable with healthy individuals. The skin of the upper arm is cleansed with ether. Two drops of the above solution are then placed on the skin about 2 inches apart, and the skin slightly abraded by the aid of a lancet, which is then disinfected, and a third abrasion made between the other two to serve as a control.

After forty-eight hours some redness and œdema result, and a papule resembling that of vaccinia soon appears at the two infected areas, but not at the control one. Within a week the pustule dries up, and the reaction subsides.

The advantage of this test is that, as there is no temperature reaction, it can be employed in pyrexial cases and in children without fear of constitutional disturbance. It has been found especially trustworthy in the first three years of life ; it is not quite so reliable after that up to ten or twelve, and still less so afterwards, especially in the very cachectic.

3. *The Ophthalmo-Reaction of Calmette and Wolff Eisner.*—These two investigators simultaneously discovered that a diagnosis of tuberculosis can be established in a very large percentage of cases in the following way :

By means of 95 per cent. alcohol a precipitate is obtained from Koch's old tuberculin. This is washed and dried, and made up in a solution of normal salt

[1] *Deut. Med. Woch.*, May 23 and 30, 1907.

solution to a strength of 0·5 per cent. One or two drops of this solution are introduced into the eye of the person supposed to be tuberculous near the inner canthus, and the eye kept open for a few seconds. A positive reaction appears in from eight to twenty-four hours, and begins with lachrymation, going on to reddening of the conjunctiva, and in severe cases to fibrinous exudation. The amount of reaction is no evidence of the severity of the disease, and varies from slight injection of the caruncle—which can only be detected by comparison with the untreated eye—to all the signs of a severe purulent conjunctivitis with œdema of the lids. The reaction usually passes off in three to four days, but may last for a week, or even longer. As a rule, little discomfort is caused, but occasionally there may be sufficient pain to require treatment. In cases free from tuberculous infection no reaction soever is obtained.

From a summary of all the published observations, it would appear that 95 per cent. of all cases suffering from active tuberculous infection give a positive reaction. Moribund cases and a few of miliary tuberculosis refuse to respond, while in cases supposed to be quiescent either a positive or a negative result may be obtained.

Any affection soever of the eye already present is an absolute-contra-indication to the employment of this test. Several accidents, such as corneal ulceration and iritis, have been reported to have resulted from its use, and have led to the employment of a solution of 1 in 200 instead of one of double this strength, as was first advocated. It is, perhaps, advisable to use a still weaker solution—say 1 in 500—in the first place, and only if this prove negative, one of a strength of 1 in 200 two or three days later. The accidents which undoubtedly did

occasionally follow the use of the 1 per cent. solution have tended to bring this test into a certain amount of discredit, but in careful hands these may well be obviated in the future; and this most valuable method of diagnosis in doubtful cases occupies a deservedly assured position.

(4) *The method of observing deviation of complement* (Gengou-Bordet effect) must be mentioned, but the difficulties of carrying out the test are too great to enable it to be employed in practical diagnosis.

(*C*) *Special Method Dsependent upon Observations of the Opsonic Index.*—These have all been referred to previously, but are here recapitulated that attention may be drawn to a few important points.

1. Simple determination of the index, repeated if necessary.

2. Determination of the index before, and at various intervals after, the production of an auto-inoculation by movement, massage, Bier's congestion, etc.

3. In women comparative determinations before and during a menstrual period.

4. Determination of the index before injection of a small dose, say 0·00002 c.c. T.R., and one day, two days, and ten days after, with a view to the observation of the extent and duration of the resulting negative phase, which in healthy people will be very slight and of short duration—viz., amount to 0·1 or 0·2 and last one or two days—in the infected it will be greater and of longer duration—viz., 0·3 or 0·4—and may last even a week or a fortnight, or longer (*vide* p. 22).

It must be noted that if the patient be infected by bacilli of the bovine type, no response may be elicited by injection with T.R. of human origin, but will be by T.R. of bovine origin. It is, therefore, perhaps best in

performing the test to use both T.R.'s and estimate the indices to both varieties of the bacillus. This failure to respond to T.R. of human origin was noted by Stewart and Ritchie in about 10 per cent. of their cases,[1] and in eleven cases of Ritchie, referred to on p. 88.

5. The absorption method of Peel Ritchie (*vide* p. 87), with diluted and undiluted, heated and unheated, sera.

The sera of two of the eleven cases there referred to which failed to give the absorption reaction with tubercle bacilli of human origin were tested with bacilli of bovine origin, and gave the characteristic reaction.

III. Types of the Tubercle Bacillus: Human and Bovine.

Assuming now that a definite diagnosis of tuberculosis has been made, before beginning a course of tuberculin inoculations it is obviously advisable that the variety of the organism at work, whether of the human or bovine, or of both types together, should be determined.

Until quite recently the very important bearing of this upon the choice of the appropriate variety of tuberculin to be employed in any given case received no consideration. Tuberculin of human origin was alone employed, and was given indiscriminately. To this cause must be imputed many of the past failures of tuberculin, and the due recognition of this most important point cannot fail to result in the near future in a great advance in tuberculin therapy.

Tuberculous cases may for this purpose be divided into two categories: (1) Those in which the bacilli can be obtained for examination and culture, whether from the sputum, urine, fæces, or purulent exudates (special

[1] *Edinburgh Medical Journal*, May, 1907.

methods for the examination and isolation of the bacilli applicable to different cases will be found in the Appendix); (2) those cases in which specimens of the bacilli cannot be obtained for examination, and indirect means of arriving at a correct diagnosis must be employed.

It now becomes necessary to consider whether it is possible accurately to differentiate the human from the bovine variety of the tubercle bacillus. Of the possibility of human tuberculosis being due to the bovine bacillus there is now no doubt. Upon that point the German and English Government Commissions and numerous independent observers are in complete agreement. Upon the possibility of always being able to say to which type a given bacillus belongs there is not the same unanimity of opinion.

Eastwood[1] says that 'the evidence of capacity for modification of the tubercle bacillus is sufficient to make caution necessary before it is concluded that a case of human tuberculosis has not originated in bovine infection, because the associated bacilli are of the Eugonic variety (*i.e.*, human type). In course of long residence in the human body, a bacillus, originally of bovine origin, might experience a modification of some of those characteristics which are met with in bacilli freshly isolated from the bovine, and owing to this modification might be indistinguishable from bacilli derived from previous cases of human disease. The differences in virulence of different bacilli, in the types of histological lesion produced by identical bacilli, and in the cultural characters of different bacilli all overlap and interweave so closely that it is impossible to find [a somewhat bold statement]

[1] Second Report of Royal Commission on Tuberculosis, vol. ii. of Appendices thereto.

an adequate scientific basis for separating these bacilli into two or more families.' To this it may be replied that within the past two years the entity of typhoid fever has been entirely upset; that no longer is the *Bacillus coli communis* boldly differentiated from the *Bacillus typhosus;* that not only are paracolon bacilli recognized, but also several varieties of paratyphoid; and that no pathologist, despite the variation in pathogenicity exhibited, not only by the different groups, but even by different members of the same groups, considers it impossible to find an adequate scientific basis for separating these bacilli into two or more families.

The cultural characteristics of typical members of the two groups are set out in the following table:

Human or Eugonic Type.	Bovine or Dysgonic Type.
1. In *broth* rapid formation of thick, tough, wrinkled pellicle, which shows no tendency to sink. If the broth be slightly acidulated to begin with, this reaction never entirely disappears.	1. In *broth* pellicle often slow in making its appearance; generally very delicate, semi-translucent and speckled with a variable number of white spots; occasionally it is opaque. It is very thin on the whole, and, with the exception of a few irregularly thickened areas, uniform. The acidity of the broth may be entirely neutralized and its reaction even become alkaline.
2. On *glycerine agar* it usually forms a dense, warty, wrinkled layer.	2. On *glycerine agar* a thin grey haze on the surface is generally all that is to be seen at the end of five or six weeks.
3. On *potato* there is rapid formation of a heaped-up richly pigmented growth.	3. On *potato* at the end of five or six weeks the growth does not consist of more than a few grey colonies or streaks.

In addition to these cultural differences, Spengler,[1] whose experience of tubercle bacilli is probably unique, considers that the two varieties present these further differences :

1. *In Morphology and Methods of Staining* (for which see Appendix).—When suitably stained the bovine bacillus is the much larger and thicker. The bovine has a thicker and sharper envelope than the human, but when stained by the ordinary method this envelope is injured by the acid and heat, being composed of a wax of low melting-point.

2. *In Sporulation.*—The bovine bacilli, by special methods of staining, may be seen to contain spores within them, while human do not (*vide* Appendix).

3. *In Agglutination.*—In pure culture they agglutinate differently. What will agglutinate the one will not the other, showing that they produce different antibodies. The serum of the human being when affected by tuberculosis usually agglutinates both, speaking for the double etiology (*vide infra*).

4. *In the Toxins.*—A patient infected principally with bovine bacilli is most sensitive to the toxins of the bovine bacillus, and one infected principally with human is most sensitive to toxins from the human.

5. *In their Localization in the Body.*—The human bacillus demands more oxygen than the bovine, hence is found nearer to the atmosphere in the tissues. They infect the lungs principally ; while tuberculosis of the intestines, kidneys, bladder, and glands is more apt to be by the bovine bacillus. When the larynx is infected, the deep ulcerations are most apt to be due to bovine, the more superficial to the human bacillus.

[1] *Wien. Med. Woch.*, 1902, No. 14 ; *Zeitschrift f. Hyg. u. Infect.*, Bd. xlix., 1905, etc.

It is perfectly obvious that very special training is necessary before even an attempt can be made to differentiate between the human and bovine bacillus; and even granting the skill, the time necessary for such an examination will, as a rule, be lacking. Where the bacilli can be obtained and isolated (for methods see Appendix), I would maintain that all experience of vaccine therapy derived from the study of other varieties of bacteria would indicate that an autogenous vaccine, prepared from cultures of the patient's own bacilli, will certainly be the one most appropriate for him. This has now been done in a number of cases, but no statistics are yet available as to the relative advantages of such a vaccine.

Should no secretion be available in which the bacilli may be examined, it is obvious that methods other than the above must be adopted in order to ascertain the variety of the infecting organism. Several methods are here available :

1. See method *C* (4), p. 104.
2. See method *C* (5), p. 105.
3. Advantage may be taken of Spengler's observation that a patient infected solely or principally with bovine bacilli is most sensitive to the toxins of the bovine bacillus, and one infected solely or principally with human is most sensitive to the toxins of the human bacillus. The patient is put to bed till the temperature chart no longer shows violent fluctuations, and tuberculin of human origin given diagnostically (see p. 99) till a definite temperature reaction is obtained, or, failing that, till the maximum dose has been given. In the former event the administration of the same or a slightly larger dose of tuberculin of bovine origin should almost at once

re-establish the temperature either to or below its former level; in the latter case it should result in a rise of temperature, which will be correspondingly depressed by another similar dose of tuberculin of human origin. Care and close observation are, above all, necessary for the success of this method.

Considerable help may be anticipated from a careful study of the several effects of therapeutic doses of the two tuberculins upon the opsonic index in a given case, but the necessary data have not as yet been worked out.

Statistical Results of Observations carried out according to the Above Methods.

1. The German Government Commission examined fifty-six cases of human tuberculosis, with the following results: In fifty cases they found the human type, in the remaining six the bovine type. These latter were all in children under seven years of age, and were affected as follows:

(1) Tuberculosis of mesenteric glands.

(2) Tuberculosis of mesenteric glands.

(3) Tuberculosis of mesenteric glands, with intestinal tuberculosis.

(4) Tuberculosis of mesenteric glands, with tubercles in spleen and pleura.

(5) General miliary tuberculosis of lungs and meninges.

(6) Acute general miliary tuberculosis.

2. Of the workers on the Royal Commission on Tuberculosis, Cobbett[1] isolated the bacilli from sixty cases, and tabulated his results as follows:

[1] Vol. ii. of Appendix to vol. i.

TABLE X.

Nature of Case.	Number of Cases.	Nature of Strain of Bacillus isolated.			
		Bovine.	Human.	Irregular.	Human→Bovine on Passage.
Phthisis with tubercular sputum ..	4	1	2	—	1
Primary pulmonary phthisis	10	—	10	—	—
General tuberculosis	1	—	1	—	—
Tuberculous bronchial glands ..	4	—	2	—	2
Cervical glands ..	9	3	6	—	—
Primary abdominal glands..	19	10	8	1	—
Joint	10	—	9	—	1
Testicle and kidney	2	—	2	—	—
Lupus	1	—	—	1	—
Total	60	14	40	2	4

Another observer gives the following results in eight cases:

TABLE XI.

Nature of Case.	Age in Years.	Bovine Type.	Human Type.
Cervical adenitis	5	+	
Tuberculous tonsil..	5	+	
Tuberculous tonsil and glands	2	+	
Meningitis and glands	3	+	
Genito-urinary	30		+
Miliary tuberculosis	21		+
Phthisis			+
Phthisis, peritonitis, and enteritis ..	61		+

Stewart and Ritchie found that 10 per cent. of all cases of pulmonary phthisis refused to respond to diagnostic test No. 4 (*vide* p. 104) with T.R. of human origin,

and now believe that these cases are due to infection by the bovine variety; while Ritchie also demonstrated by means of test No. 5 (p. 105) that out of eight cases of abdominal tuberculosis, five were due to infection by the bovine type and three to the human; and of four cases of cervical adenitis, all were bovine in origin—results which agree well with those already quoted. Taking these in conjunction, it would appear that adenitis is slightly more frequently due to the bovine than to the human type, and that this holds the more strongly in the case of young children.

Insufficient observations have been made in other varieties of tuberculosis, excepting the pulmonary, to justify any definite conclusions being drawn.

Spengler[1] has made a most careful study of 112 cases, with the following results. Inasmuch as these were all cases of pulmonary tuberculosis, and he adopted special methods, his results must stand by themselves.

Sixty-eight cases, or 60·8 per cent., showed a symbiotic working of the human and bovine types. All were chronic cases.

Twenty-two cases, or 19·6 per cent., had exclusively human bacilli. All showed fever, and offered a bad prognosis.

Six cases, or 5·3 per cent., had almost exclusively bovine bacilli. All suffered from fever, but with a better prognosis than those infected by the human variety alone.

Sixteen cases, or 14·3 per cent., showed only 'splitter' (see Appendix), but no bacilli. Of these—

Seven had only human bacilli 'splitter';
One had only bovine bacilli 'splitter';
Eight had both human and bovine bacilli 'splitter.'

[1] *Wien. Klin. Rundschau*, No. 33, 1906.

He considers that the two varieties, human and bovine, are antagonistic in action, causing a chronic course. Those cases where only one variety is found are the most virulent and difficult to treat, and of these the human is more virulent than the bovine. He also considers that they require different immunizing agents, and therefore that in cases where both varieties are present iti s necessary to determine which has the greater significance, and to attack that one with the appropriate agent.

IV. Choice of Tuberculin Appropriate to a Given Case.

Assuming for the time being the possibility of determining the variety of the bacillus infecting any given case, it becomes necessary to consider which is the appropriate tuberculin to employ.

Spengler in Germany, Pottenger in America, and Raw in this country, argue as follows: Romburg and Behring have shown that cattle, which are for practical purposes immune against the human variety, can be most completely immunized against infection by the bovine type by inoculation with the human type; therefore, conversely, human beings can be best immunized against infection by the human type by means of tuberculin of bovine origin, and *vice versa*. Theoretical objections to this reasoning are:

1. That bovines and humans are not quite on a par; the human type cannot produce generalized tuberculosis in bovines, but the bovine type can and does in humans.

2. That this is opposed to all the theories of immunity, and still more opposed to all the experiences of vaccine therapy with other organisms, which has demonstrated

the great advantages possessed by a vaccine of the patient's own organisms, even over one of the same identical organism from another source. This would seem to indicate clearly that not only is a tuberculin of bovine origin inappropriate to an infection by the human type, but that a tuberculin prepared from the patient's own organism will have a definite advantage over a tuberculin prepared from the same variety from any other source.

However, an ounce of practice is better than a ton of theory, and the results of these observers' practical experience require consideration. Acting, then, upon the theory that the human and bovine types of the bacillus are opposed to each other in every way, and that a human type infection is best combated by a tuberculin of bovine origin, and *vice versa*, Spengler devised a system of therapy (uncontrolled, of course, by opsonic index determinations) upon the following lines: Having determined the variety of organism at work by means of laboratory and clinical observations, he gives an injection of a diagnostic dose of bacillary emulsion from the other variety of bacillus. If the diagnosis is correct the temperature, if elevated, usually falls, and the patient will declare that he feels better; if, on the other hand, the diagnosis is wrong, then the remedy acts as a toxin, and the patient experiences an increase in the symptoms.

When the patient feels better after the injection of a vaccine, this preparation may be taken as the vaccine suited to the case, and may be used therapeutically. After one has been used for some time the other is employed, till the patient is immunized to both. In proof of the antagonistic working of these two vaccines, and what seems to speak very much for this therapy, is the

fact, adduced by Pottenger,[1] that if one preparation is injected, and it proves to be the toxin for the patient instead of the vaccine (as Spengler calls the one which does not act toxically), a dose of the other may be injected at once, and it will serve to counteract the toxic action of the first preparation. (See Figs. 28 A and B, *loc. cit.*)

This therapy has proved very successful in the treatment of fevering cases, and also in the treatment of such complications as tuberculosis of the larynx, intestines, and kidney. While admitting the full importance that must necessarily be attached to the opinions and clinical experience of such observers as Spengler and Pottenger, it must be pointed out that the value of this method over the older one has not been actually demonstrated by comparative statistics.

Theoretically, several criticisms may be made against it upon *a priori* reasoning :

1. It is opposed to all experience in other bacillary infections, as mentioned before.

2. Spengler's statistics show that in 60·8 per cent. of all cases of phthisis there is a symbiotic working of human and bovine bacilli. Therefore in 60·8 per cent. of all cases this therapy results in the simultaneous administration of the toxin to one of the organisms at work and of the antitoxin to the other. Thus in time the infection should be reduced to a simple one by one variety, which Spengler himself says always affords the worst prognosis. It is true that afterwards the patient is immunized to the other variety as well, but only after some time has elapsed.

3. That the *toxin* of one variety of bacillus is the better neutralized by the antitoxin elaborated in response to the

[1] 'Pulmonary Tuberculosis,' p. 179.

injection of the other variety of bacillus is no proof that the more powerful *antibactericidal* substances for the one variety are elaborated in response to injections of the other variety. Of course it may be so, but iti s not necessarily so; and it may well be that the general reaction obtained by the injection of a diagnostic dose of the tuberculin homologous to the infecting variety of bacillus is a response to the toxic products formed by the death of the bacilli at the infected focus, and so a measure of the resultant bacteriolysis. That a fall of temperature will now result upon inoculation with a vaccine of the other variety of bacillus is still explicable upon Spengler's observation that the toxins of the one are neutralized best by the antitoxins elaborated in response to an injection of the other variety.

There is some evidence to support this possible explanation. On p. 93 of the first edition the author announced that he was conducting a series of cases upon new lines. For over a year past he has been treating cases of adenitis, pulmonary phthisis, and ocular tuberculosis with a vaccine containing the T.R.'s of human and bovine origin mixed in equal proportions. According to Spengler's view, the two should have neutralized each other's action, and practically no effect have been produced. Actually the results have appeared to be so markedly superior to any he had previously obtained that the use of the ordinary T.R. has been completely given up in favour of this mixture. The series of cases treated is, however, too small as yet to enable one to speak definitely as to the real relative value of the method. It is, however, hoped that other observers will give this procedure a fair trial, obviating, as it does, the necessity of determining the variety of bacillus at work.

Stone and Miller,[1] in a most thoughtful paper, have drawn attention to other theoretical considerations relative to immunization by means of the tubercle bacillus and its products. They tabulate the various preparations as follows. Of course, either the human or the bovine strain may be the source for each :

A. Toxic media products	Old tuberculin (Koch) Purified old tuberculin Bouillon filtrate (Denys)	Productive of *antitoxic* immunity.
B. Endotoxic cellular products ..	New T.R. (Koch) : part cellular product Bacillary emulsion : total cellular product	Productive of *antibacterial* immunity.

They then point out that, inasmuch as the protective influence of the tuberculins of Class A. is largely antitoxic and not bacterial, it would seem that the use of the filtrate products would bring the most benefit in cases suffering from pure tuberculous toxæmia ; but toxæmia is not a prominent feature of uncomplicated tuberculosis—at least, in early stages. How important it may be in advanced cases remains to be settled. Without secondary organisms (influenza bacillus, pneumococcus, staphylococcus, and streptococcus) it is probable that toxic features with softening and dissolution of tissue would be a much less important factor in the course of the disease. Maragliano having shown that in antitoxic value the serum of man is much greater than the serum of cow, goat, or horse, but in antibacterial power that the reverse is the case, it would appear that in man the attempt should first be made to raise the antibacterial value of his serum, since normally this is lower than the relative immunity existing towards the products of the germ.

[1] *Medical Record*, March 28, 1908.

They therefore suggest that better results than at present obtained might be secured by employing a combination of bacillary emulsion with bouillon filtrate (Denys).

V. Conduct of Case of Pulmonary Tuberculosis undergoing Vaccine Therapy.

Assuming that the diagnosis of tuberculosis has been duly made, the variety of bacillus at work determined, either by direct or indirect means, and the variety of tuberculin to be employed decided upon, the important question remains, shall the physician rely entirely upon clinical symptoms as his guide, and employ his remedies rather according to rule of thumb, or shall he be guided by determinations of the opsonic index? As will be shown in Section 6 of this chapter, Spengler, Trudeau, Pottenger, and many others have achieved brilliant results, relying upon clinical signs alone, and employing doses of such magnitude and at such intervals as are utterly opposed to opsonic principles. Pottenger[1] says: 'If the negative phase were as important as Wright maintains, we would have killed our patients by the dosage which we have been employing. On the contrary, those who have used tuberculin and its allies intelligently, depending upon clinical symptoms and local signs as the guide to dosage, have been able to produce the best results that have been obtained in the treatment of this disease. If a negative phase does follow every injection of tuberculin vaccine, we must assume that it is of less importance than has been attributed to it. While we would in no way minimize the value of Wright's work, —for we believe it furnishes us a key by which we may

[1] 'Pulmonary Tuberculosis,' p. 197.

solve many of the problems associated with the phenomena of immunity and the treatment of infectious diseases—yet we do not believe that the fact that many careful clinicians are not so situated as to be able to avail themselves of the knowledge obtained by estimating the opsonic content of the blood should deter them from giving their patients the benefit of intelligent treatment by specific products made from the tubercle bacillus. It must be said, however, that an increased experience seems to show that results may be obtained with smaller doses than we have been wont to employ.' This is the opinion of a thoroughly scientific and unprejudiced mind; yet there is one obvious comment to be made: the clinical knowledge and the power of accurate observation brought to bear by such famous specialists as these is as rare as, or even rarer than, the capacity for determining the opsonic index accurately, and the observations needed are little, if any, less laborious. The one is as difficult for the busy general practitioner as the other, and while he can have the index determined for him, he cannot himself spare the time even to acquire the special clinical knowledge, much less to employ it, in the case of every phthisical patient. With a disease so widespread as phthisis, discussion of ideals is of little use to the many; the treatment of the vast majority of cases is, and probably will remain, in the hands of the general practitioner. And I do not propose to discuss the relative merits of treatment according to clinical signs, as practised by famous specialists, and of which statistical results are available, and of treatment guided by determination of the opsonic index, also by specialists, and of which sufficient statistical results are as yet lacking.

The last word has as yet by no means been said as to

the vaccine therapy of pulmonary tuberculosis. Opsonic methods have taught valuable lessons, and will probably teach more, but there is an undoubted danger of overestimating the importance of opsonic-index estimations, for, after all, opsonin is only one of the protective substances elaborated by the body, and of its importance in the various infections relative to the other immunizing agents we as yet know nothing. The more especially true does this appear to be in the case of the tubercle bacillus and phthisis.

The pure clinician will continue for the present to conduct his procedure under the guidance of clinical symptoms, correcting his judgment by the lessons of opsonic methods, especially as regards dosage; the opsonic expert will continue along opsonic lines, but be ready to modify his present opinions, while the happy few who are possessed of both capabilities will probably elaborate methods to supersede those of both the others. It remains for the general practitioner to decide whether he will disregard the solemn warnings of Wright,[1] and, while paying due regard to the lessons learnt from opsonic methods as regards dosage, rely upon his powers of clinical observation, or distrusting his own powers and fearing untoward results, rely upon the index determinations of a practised pathologist as his guide. The financial position of the patient will need to be considered. Should it be capable of bearing the strain, I think that in the present state of our knowledge the best results can only be expected in every case under the guidance of the opsonic index, and the physician will be well advised who has this estimated every week. Good results are, however, often to be obtained without it, and inability to secure its guidance, either from financial reasons or otherwise, should not

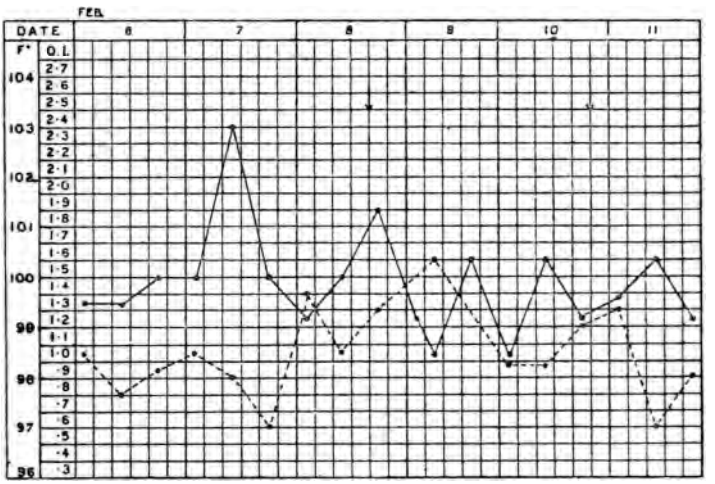
[1] *Practitioner*, May, 1908.

deter the physician from giving the patient the benefit of intelligent treatment by specific products under the guidance of clinical symptoms alone.

Temperature as a Guide in Tuberculin Therapy.

The statement used to be made that temperature and pulse bore no relation soever to opsonic index; this has

CHART XI. (A. C. Inman).



This chart shows how temperature and opsonic index were correlated in a case of pulmonary phthisis. The two will be seen to have moved together but in reverse directions, a more or less constant phenomena.

now been shown to be quite wrong. The negative phase resultant upon the injection of any bacterial vaccine is, as a rule, ushered in by rise of temperature (see Chart XI.), while the observations of Wright himself, in septicæmic cases, and of Latham, Spitta and Inman,[1] in pyrexial

[1] Proceedings of the Royal Society of Medicine, April, 1908.

and apyrexial phthisis, clearly show that the opsonic index fluctuates with the temperature, but in an inverse direction. The latter observers also state that (1) when the temperature has been fluctuating from 97° F. to 98·4° F., and then remains level at 98° F., the opsonic index rises; (2) when the temperature, previously level and normal, or subnormal, rises to 99° F., the index falls; (3) when the temperature is persistently high the index is persistently low; (4) when the temperature, although remaining at about the same high level, fluctuates to a less degree, there is an improvement in the opsonic index.

It is partly to auto-inoculations that these rises of temperature are to be ascribed, and the importance of either obviating or controlling the auto-inoculations by rest in bed and various therapeutic measures, such as increasing the coagulability of the blood by doses of calcium salts, becomes more than ever apparent.

Immunization under Guidance of Clinical Symptoms.

Such measures having been taken for the good of the patient as clinical experience has decided to be appropriate, such as rest in bed, good food, and plenty of fresh air, immunization may be proceeded with, employing one or other of the various preparations of tuberculin, as follows:

T.A. (Old Tuberculin Koch).—This, as said before, is one of the toxic media products, and is now chiefly employed for the diagnostic test. It may be made from either human or bovine strain, the latter being known as P.T.A. It is used therapeutically as follows:

For patients in the first and second stages, in whom prognosis is still good, and who are free from fever, the initial dose is from 0·0001 c.c. to 0·001 c.c., to be gradually increased by the same amount, and given every third or

fourth day, according to symptoms, until 0·005 c.c. has been given, when the increase may be by 0·002 c.c., until 0·01 c.c. is reached, when the increase may be more rapid. A feeling of nervousness, malaise, or aching, either with or without a slight rise of temperature, is to be taken as a sign of reaction. The dose should then not be repeated until this has disappeared, and the amount should not be increased until this amount, when injected, fails to produce these symptoms. If all goes well, the dose may be increased thus : 0·015, 0·02, 0·03, 0·04, 0·06, 0·08 c.c., given at properly spaced intervals ; but this should not be attempted by one who does not understand the remedy well. Sometimes patients are very sensitive to tuberculin, and the dose can then only be increased very cautiously, it taking even one or two months to attain a dosage of 0·001 c.c.

In cases in the third stage the initial dose is 0·00001 c.c., and it will often be found impossible to raise the dose beyond 0·001 c.c. to 0·01 c.c. in such cases without producing a reaction.

In almost all cases the maximum dose should be repeated several times at increasing intervals of weeks after the patient is apparently cured. Bandelier and Roepke[1] state that, as experience increases, the contra-indications to this line of treatment grow fewer and fewer, and that they have treated with success, or, at any rate, marked improvement, advanced cases with hectic fever, purulent expectoration, cavities in the lungs, anæmia, and emaciation.

Tuberculin (Denys) is, like the above, a toxic medium product. It is a filtrate made from the bouillon on which the bacilli have grown, and is prepared without being

[1] *Lehr. der Spezif. Diag. u. Ther. der Tuber.*, Würzburg, 1908.

subject to heat, and is not concentrated like Koch's old tuberculin.

The pure tuberculin is taken, and seven successive dilutions made, each of a tenth of the strength of the preceding, so that the final, or No. 7 dilution, contains 0·0000001 c.c. of the original tuberculin in each c.c. This is the initial dose in febrile cases ; in a febrile case 1 c.c. of the No. 4 dilution = 0·0001 c.c. of the original tuberculin, is employed.

In either case the increase in dosage is by 0·1 c.c. at intervals of three to four days for the smaller doses ; as the higher doses are reached, five or six days must elapse, and for the last three or four doses, when the pure tuberculin is being used, intervals of a week or ten days must be allowed. The final dose is 1 c.c. of pure tuberculin. If no intolerance be evidenced, the course of treatment will extend over six months, but when reaction occurs it may need a year. If it does appear, it is necessary to await its disappearance, and begin again with half that dose. Reactions occur the more readily at doses between 0·0001 and 0·001 c.c. Denys refers to 2,000 cases as having been treated successfully by him according to this procedure.

T.O. (human) and *P.T.O.* (bovine) correspond in properties to the old tuberculin. They are composed of the toxic products removed by treating the comminuted bacilli with water in the preparation of T.R.

Spengler's P.T.O. is not concentrated by heat ; he finds it much less toxic for human infections than the corresponding preparation from the human type, and at the same time more active in the stimulation of the machinery of immunization, as measured by the power to increase the specific agglutinins of the blood.

The procedure is exactly the same as for T.A. Spengler,

however, considers the least feeling of warmth at the site of injection as sufficient to negative a fresh injection until this sign of reaction has subsided. Bandelier and Roepke (*loc. cit.*) report satisfactory results in 178 cases. Fever and the presence of mixed infection are not contra-indications to its use, and Spengler believes that only patients *in extremis*, or with very acute pulmonary phthisis, are beyond its reach.

T.R. (human) and *P.T.R.* (bovine) are endotoxic cellular products prepared from the human and bovine types respectively. They are probably the mildest of all the forms of tuberculin, and are productive of antibacterial, and only to a slight extent of antitoxic immunity. They are, therefore, especially suitable for the treatment of patients who are very sensitive to T.A. or T.O., and may be used to pave the way for the use of these latter. The initial dose is 0·0001 to 0·0002 c.c., and may be given every other day at first. It can usually be doubled at each dose, until 0·01 c.c. of the original has been given. After this the injections should be further apart, and the increase in dosage be as follows: 0·015, 0·025, 0·035, 0·06, 0·08, 0·1 c.c. After 0.5 c.c. has been given the dose should be given only once a week; 0·1 c.c. is rarely exceeded. At the least sign of reaction the dose must be withheld until all reaction has disappeared, and it must not be increased until the patient fails to react to the dose which has once caused a reaction.

B.E. (human) and *P.B.E.* (bovine) are total cellular products, and consist of an emulsion in 50 per cent. glycerine of the pulverized bodies of the bacilli, without prior removal of toxins soluble in distilled water. They contain 5 milligrams of bacillary substance per c.c., and are probably the most active of all the preparations. The

objection to them is the difficulty of absorption of the bodies of the bacilli, which may remain in the tissues, act as mechanical irritants, and cause a pseudo-abscess containing sterile sero-purulent fluid. The initial dose is 0·0005 c.c., and is repeated every second or third day, each time increasing the amount given by two or three times the amount previously given. When a reaction is produced, the injections are given at longer intervals—say, every six to eight days. They are increased till 1 to 2 c.c. of the original is reached, but these large doses are given only every two to three weeks, on account of the slowness of absorption. In pyrexial cases the initial dose is not more than one-tenth of that indicated above. These preparations are the ones most favoured by Spengler, and are employed by him as indicated on p. 114.

Immunization under the Guidance of the Opsonic Index.

Despite the criticisms levelled against the accuracy of present methods of determining the opsonic index, this must be admitted, even by the most biassed, as the most scientific means of attempting to secure immunity. Even should the time and amount of dosage of any particular injection not be determined by *prior* determination of the index, a study of the whole opsonic curve, taken in conjunction with the temperature chart, clinical signs, and general condition of the patient, will afford the most valuable information as to the progress of the patient and his immunizing responses. The first essential that must be secured before full use can be made of this method is arrest, as complete as possible, of all auto-inoculations by rest, physical and mental, and other therapeutic measures, among which may be mentioned

administration of full doses of calcium salts. A reduced and regular temperature, and steady opsonic index—it may be at a level higher or lower than normal—will indicate cessation of auto-inoculations and return to a more or less strictly localized infection. The index having been estimated at the same time upon two or three consecutive days, not only to the human, but also to the bovine type, and the maintenance of a steady level assured, a minimal dose of, say, 0·00001 c c. of the appropriate tuberculin is given. Which is the appropriate tuberculin must be considered. Raw[1] says, for pulmonary phthisis the T.R. of bovine origin. Spengler (*vide* p. 114) determines it experimentally by the administration of a diagnostic dose of tuberculin of known origin and the observation of the temperature reaction. The author, in view of Spengler's bacteriological studies, whereby he shows (p. 112) that 68 per cent. of all pulmonary cases were infected by both the human and bovine types, and a recent limited clinical experience, would urge that a mixture of human and bovine T.R.'s in equal amounts will best suit the greater majority of cases, and will suit the remainder as well as any other.

Whether the view of the antagonism of the two strains be correct or not, the advisability of estimating the index towards *both* strains is obvious. This, then, is done upon the day following the injection, and, if possible, upon each day up to the tenth, that the precise amount of reaction and duration of negative phase may be estimated. As to how the results are to be interpreted as a measure of dosage, etc., see p. 26.

The object now is to maintain the index at as high

[1] *Lancet*, February 15, 1908, p. 481, etc.

and steady a level as possible, and to bring as full a supply as possible of this actively immunizing blood to the infected focus. The injections are therefore repeated at suitable intervals, which may vary from ten to twenty-one days, and in adequate doses, and the coagulability of the blood diminished, if necessary, by doses of citric acid. The dosage is steadily increased as indicated by the index, but is rarely raised above 0·0002 c.c. In apyrexial cases where there are no auto-inoculations occurring, this treatment may be conducted while the patient is going about his daily work.

In cases complicated by secondary infections, much better results than are now obtained will probably be secured by a simultaneous attack upon the staphylococci, streptococci, pneumococci, micrococcus catarrhalis, Friedländer's bacillus, *B. influenzæ*, etc., which may be present.

Immunization by Means of Auto-inoculations induced by Means of a Scheme of Graduated Exercise.

has been warmly advocated by Patterson.[1] Inman[2] has studied the scientific aspect of this question, and finds the explanation of the excellent results achieved by Patterson in the effects produced upon the opsonic index. It would appear that much benefit accrues to convalescent patients by means of such exercises, carefully graduated under the guidance of temperature chart, clinical signs, and opsonic index, and that a more speedy and complete cure is effected.

[1] *Lancet*, January 25, 1908, p. 216. [2] *Ibid.*, p. 220.

Immunization according to the Lessons learnt from a Study of Opsonic Methods, but not under the Guidance of the Opsonic Index.

This obviously must be the resort of many busy general practitioners, who have neither the time nor skill necessary for doing the index themselves, and whose patients are not in such a financial position as to warrant the work being done by a highly-trained pathologist. That the best results will be secured is an obvious impossibility, but this is no reason why the patient should be deprived of the benefits likely to accrue from a course of therapeutic inoculations intelligently conducted. Even pyrexial cases, and others where auto-inoculations are occurring, can derive little harm, and may derive much good. A thoroughly safe and reliable scheme of treatment remains to be worked out, but the observations of Spengler, that pyrexia due to the human strain may be reduced by a vaccine of bovine origin, and the suggestion of Stone to attack simultaneously the bacilli and their excreted toxin by the combination of the appropriate T.R. with, say, Denys' tuberculin deserve full consideration. My own procedure at present (controlled, however, by index determinations) is to use mixed human and bovine T.R.'s for all cases; and in those where toxæmia is an important factor to combine minute doses of Denys' tuberculin with the T.R.'s. I can only say that a very limited experience has given the utmost satisfaction.

In *apyrexial* cases, then, the following provisional scheme might be laid down for use without index determinations, but controlled by common sense and close clinical observation:

Begin with a dose of 0·00001 c.c. mixed human and bovine T.R. Repeat this in seventeen to twenty-one days, unless contra-indicated, and again after a similar interval. Fourteen days later give 0·00002 c.c. of the same mixture, and repeat in fourteen days. If satisfactory improvement, continue for one or two more similar doses at similar intervals. If neither improvement nor the reverse, increase dose to 0·00003 c.c. at twelve days' intervals. If ill is resulting, carefully consider whether it is due to the treatment or in the natural course of things, and decide whether to continue or not.

In this way a dose of 0·0001 to 0·0002 c.c., repeated at ten days' intervals, may be attained in about nine months. If cure has apparently resulted, then slowly diminishing doses may well be employed at lengthening intervals for another six months.

In *pyrexial* cases take all possible steps to reduce pyrexia and control auto-inoculation; then proceed as before, with extra caution, combining, however, with the T.R.'s quantities of Denys' tuberculin, very minute at first, but increasing at each dose in much greater ratio than the T.R. Thus, the initial dose may be 0·0000001 c.c., going on as follows: 0·0000002 c.c., 0·0000003 c.c., 0·0000006 c.c., 0·000001 c.c., 0·000002 c.c., and so on until ultimately a dosage of even 0·001 c.c. has been attained in combination with 0·0001 to 0·0002 c.c. of each T.R.

This scheme, guided by common sense and controlled by close clinical observation, will, I think, be found perfectly safe, and productive of good results.

Results of Vaccine Therapy in Pulmonary Tuberculosis.

A. By Methods controlled by Clinical Symptoms.—Pottenger,[1] after pointing out that culture products are to be used in *tuberculosis*, and that they are not represented as having any influence over dead tissue, or as being able to regenerate cells that have been destroyed, and therefore that their proper sphere is in incipient cases before mixed infection or breaking down with absorption occurs, gives the following statistics of the comparative results obtained in first-stage tuberculosis by sanatorium methods pure and simple, and by sanatorium methods supplemented by tuberculin therapy according to the methods outlined on p. 125 :

Four observers treated 611 first-stage cases with all the advantages of sanatorium treatment, and apparently cured 391, or 64 per cent.

Ten observers supplemented sanatorium treatment with tuberculin therapy in 589 similar cases, of which 496, or 84·2 per cent., were apparently cured.

Pottenger considers that these are quite sufficient cases upon which to base an opinion, and considers that culture products certainly stand the test and accomplish that for which they are recommended—namely, the cure of pure tuberculosis.

Trudeau's Results.

From 1890 to 1901 Trudeau in America employed inoculation treatment in cases of pulmonary phthisis. The adjoined table is a comparison of the results obtained

[1] 'Pulmonary Tuberculosis,' p. 343.

by pure sanatorial measures with those supplemented by inoculations of tuberculin.

TABLE XII.

(1) Cases treated (Non-Tuberculin).	(2) Cases treated with Tuberculin.	Advantage to (2) over (1).
1,367	143	
Alive, 38·0 per cent.	Alive, 58·0 per cent.	20·0 per cent.
Dead, 36·6 ,,	Dead, 33·0 ,,	3·6 ,,
Balance untraced		

INCIPIENT CASES ONLY.

(1) Cases treated (Non-Tuberculin).	(2) Cases treated with Tuberculin.	Advantage to (2) over (1).
Alive, 61·0 per cent.	Alive, 76·7 per cent.	15·7 per cent.

Turban's results at Davos Platz[1] have been as follows :

In the first stage his results were such as led him to say : 'Now, if we compare the results in early cases in which tubercle bacilli were found in the sputum, the result is substantially in favour of tuberculin treatment.

'Of cases in the second stage 48 were treated with tuberculin ; 9 died within two years of treatment ; 3 died within three years of treatment and more ; 16 were alive six years after treatment ; 5 more alive five years after treatment ; 3 more alive four years after treatment. In all, 36 were alive. Thus, of 48 cases 36 were alive and 12 dead. Of 152 cases treated in the ordinary way, 45 were dead and 107 alive ; but the figures show greatly in favour of tuberculin treatment, because of the 107 alive a great number (49) were under treatment more than one or two years.

[1] *Weicker. Beit. z. Frage der Volksheilstaetten*, p. 22.

'Of cases in Stage III., 21 cases were treated with tuberculin. In 8 there was tuberculous laryngitis; 9 cases survived five years; 3 more survived four years. Only 5 out of 21—or 25 per cent.—died within two years; 3 were quite well six years after. In all 5 were well.

'Of cases treated in other ways, 61 out of 84 died, and of these, 41—or nearly 50 per cent.—died within two years. Compare this with 25 per cent. under tuberculin treatment.'

Thus, even in the second and third stages of the disease, which do not strictly fall within the zone of tuberculin treatment, a great advantage is seen to exist on the side of vaccine therapy. As regards mixed infection, which Pottenger points out exists in cases displaying fever of even mild degree, and which doubtless has its influence on the tuberculous process in many cases where no rise of temperature exists, he says:[1] 'I do not doubt but that the true remedy will be obtained in a vaccine made from the cultures taken from the strain of the micro-organism found in each individual patient. The results which we have had so far in our endeavours to treat in this manner are very encouraging.' Tuberculin alone can no more be expected to work impossibilities than can antidiphtheritic serum in moribund cases of diphtheria.

Results Achieved by Vaccine Therapy Controlled by Determinations of the Opsonic Index, or according to the Methods which Experience in Opsonic Work indicated.

The opsonic method has been upon trial for far too short a time to enable anything like reliable statistics

[1] P. 261, *loc. cit.*

to be collected. Nothing more than the impressions gained as to its value by different observers can be adduced in its favour. The most complete series of cases so far published are those of Turton,[1] who describes the results obtained in 26 cases of tuberculosis of lungs and pleura, in 19 of which control by the index was employed.

In 6 early cases without great lung destruction or severe constitutional disturbance the disease was apparently arrested, there being no abnormal physical signs or symptoms for six months. Their gain in weight respectively was 19, 13, 17½, 3, 12½, 14 pounds.

In 6 cases, of which 2 were far advanced, with great loss of weight and constitutional disturbance, great improvement occurred. Symptoms, however, were still present, or six months had not elapsed since apparent cure. Their gain in weight respectively was 35½, 13, 17, 7, 23, and 38 pounds.

In 6 cases there was some improvement in general health, and the signs and symptoms were ameliorated, but the result was not entirely satisfactory. These were most severe cases of long standing, with considerable lung destruction or some complication, their gain in weight respectively 3, 3½, 0, 5, 8, 0 pounds.

In 3 cases there was little or no improvement, but they were very unfavourable cases, the home surroundings being very unsatisfactory, disease extensive, and general health rapidly failing.

Five cases died either during or after suspension of treatment, but were practically hopeless from the first, and were only injected as a last resort.

All these cases were treated out of hospital, in some

[1] 'International Clinics' (eighteenth series), vol. ii., p. 28.

cases with very unsatisfactory home surroundings; and almost all had to carry on their usual occupations. Besides the tuberculin, cod-liver oil and occasional tonics were the only remedies used.

In the successful cases the clinical results are great improvement in general health, gradual fall in evening temperature, return of appetite, and increase in weight. The cough gradually becomes less troublesome, and the sputum reduced in quantity; the tubercle bacilli become fewer, and finally disappear. The physical signs become less marked, and where lung destruction has been great are replaced by signs of fibroid lung. In slighter cases all physical signs may disappear. While the patient is doing well, a gradual fall of the evening temperature is one of the most striking features. In some cases a fall of a degree or so occurs during the several days immediately following an injection, to rise again slowly as the next becomes due, after which it again falls. This is only seen in some cases, and, Turton says, is independent of the index. The temperature he does not consider to be a trustworthy guide. His doses varied from 0·0001 to 0·001 c.c., chronic cases having the larger doses at the longer intervals—say, 0·0005 c.c. every twelve to twenty days—while acute cases did better on a dose of 0·0002 c.c., repeated in from seven to twelve days. It cannot be too strongly emphasized that, if an accurate estimate of the true value of index determinations in the treatment of pulmonary tuberculosis is to be formed, observers must divide their cases up methodically into classes, as is done by Trudeau, Pottenger, Turban, and others, and the subsequent histories of the cases carefully watched for a term of years.

The Indices of 'Cured' Sanatorium Cases and the Question of their Injection.

Lawson and Stewart[1] examined twenty-five cases of pulmonary phthisis 'cures.' In five of these the index was between 1·1 and 0·9; in the other twenty it was 0·8, or under. Twenty-three of these elected to be injected, with the results shown in Table XIII.

TABLE XIII.

Case.	Index before Injection.	Index after Course of Injections.	Number of Injections.
1	1·0	1·1	1
2	0·9	1·4	3
3	0·9	1·4	3
4	0·9	1·2	3
5	0·8	1·4	3
6	0·8	1·0	4
7	0·8	1·3	5
8	0·8	1·1	1
9	0·8	1·0	3
10	0·8	1·2	2
11	0·7	1·1	4
12	0·7	1·5	3
13	0·7	1·0	2
14	0·7	1·3	3
15	0·7	1·3	4
16	0·7	1·2	3
17	0·7	1·3	3
18	0·7	1·3	4
19	0·7	1·3	4
20	0·5	1·1	5
21	0·5	0·8	2
22	0·5	1·5	4
23	0·5	1·1	5

The additional rise in antibacterial substances obtained by the inoculations subsequent to a long course of climatic

[1] *Lancet*, December 9, 1905, p. 1683.

and sanatorium treatment is very striking. Whether such cases with abnormally low indices are especially liable to relapse we know not, but Lawson is strongly of the opinion that no case of apparently cured phthisis with a low index should be discharged from the sanatorium until the index has been raised.

Vaccine Therapy in Other Forms of Tuberculosis.

1. *Tuberculous Adenitis.*—Of the frequency of tubercular adenitis, often unrecognized in children, there is little need to dilate. Thus, MacConkey and MacFadyen found virulent tubercle bacilli present, usually in the mesenteric glands, of about 25 per cent. of children who died from non-tuberculous causes. In infants dying of tuberculosis Steiner and Newieter found the lymph glands affected 299 times in 302 post-mortems, the bronchial glands being involved 286 times. Rilliet and Barthez found lymphatic glands involved 248 times in 312 cases ; and Northrup every time in 125 cases. Not only are the glands involved, but they are the first to show the disease in a large majority of cases, if this can be inferred from the fact that the glands show the most advanced processes. All cases of tuberculosis of the glands, however, do not show tuberculosis elsewhere, nor are all enlarged lymphatic glands tuberculous (about 60 per cent. are). Steffen, however, says : ' Healthy lymph glands are not attacked by tuberculosis. They are predisposed thereto when they are swollen, succulent, and infiltrated, and in a condition of hyperplasia.' While Osler says : ' A special predisposing factor in lymphatic tuberculosis is a catarrhal inflammation of the mucous membranes, which in itself excites a slight adenitis.'

The extreme importance of putting all children, and especially infants, under the best hygienic conditions is thus obvious, while the advisability of applying the tuberculin test, best by means of Pirquet's cutaneous reaction, in all cases where glands are chronically enlarged, the nutritional condition bad, and the child unduly pale or peevish, deserves earnest consideration, in view of the fact that a large percentage of those who have enlarged glands during childhood develop tuberculosis in later life.

Variety of the Bacillus Responsible.—From the bacteriological findings upon pp. 110, 111 and 112, it appears that in thirty-nine cases the human type was isolated eighteen times and the bovine twenty-one. In so far as one can deduce from so few cases, it thus appears that two varieties are found with about equal frequency. It is therefore obvious that if either a T.R. of human origin, or that of bovine origin, be employed invariably, it will, strictly, be the most appropriate tuberculin in only 50 per cent. of the cases. It therefore becomes necessary either to determine which is the right tuberculin, according to one or other of the methods outlined on p. 109, or to adopt the suggestion of the author, and always employ a mixture of the two T.R.'s in equal proportions ; this latter is the less scientific, but is perhaps the more easily workable scheme.

Once the diagnosis has been made that enlarged glands are tuberculous, it becomes incumbent not only to place the child under the best possible hygienic conditions, but also to submit it to a course of tuberculin treatment, in view of the almost uniformly successful results thereby obtained, and so prevent subsequent caseation and sinus formation, and perhaps pulmonary or some other serious form of tuberculosis.

Wright, White,[1] Western,[2] Rivière,[3] Loveday and Ramsbottom,[4] and many others, have published most satisfactory results, despite the sole employment of T.R. of human origin, which, as said before, cannot have been always appropriate.

When caseation is present, prolonged treatment may be necessary, and perhaps surgical interference. If liquefaction be a feature, an extensive operation may be sometimes obviated by the preliminary raising of the index to 1 or over, and the passage of a tenotome into the caseous mass and the expression of the contents.

Sinuses may be aided by the additional treatment of a vaccine of the secondarily infecting organisms, scraping, and perhaps the application of hypertonic solutions of common salt and citric acid, to assist transudation of lymph rich in opsonin.

As in the case of pulmonary tuberculosis, the best results will almost certainly be attained under the guidance of the opsonic index. Should this not be available, then an initial dose of 0·00001 c.c. of each T.R. may be repeated, and increased at such intervals as the clinical condition indicates, much upon the lines already laid down under pulmonary tuberculosis.

2. *Tuberculosis of Bones and Joints.*—Far too few observations as to the variety of bacillus at work have as yet been made to enable any definite conclusion to be drawn, but it may be noted that in the instance of all ten cases cited on p. 111 the human variety was found.

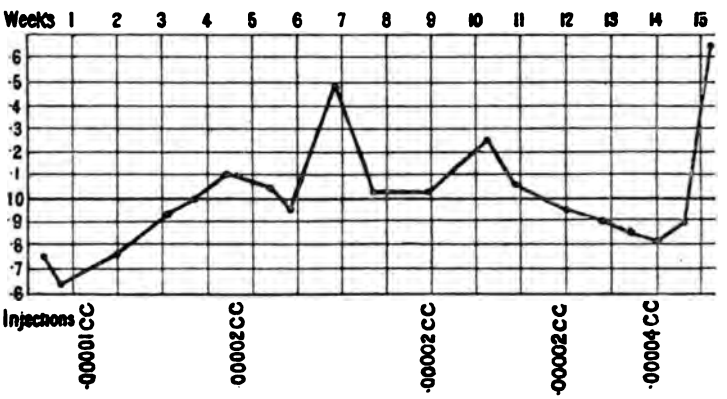
For a case of early joint disease, splints, rest, Bier's

[1] *Journal of Medical Science*, Dublin, September 2, 1907, p. 161.
[2] *Lancet*, November 23, 1907, p. 1449.
[3] *British Medical Journal*, October 26, 1907, p. 1131.
[4] *Medical Chronicle*, June, 1908, p. 145.

congestion, and tuberculin will probably suffice to effect cure. Should the disease be advanced, and the surgeon decide upon scraping or excision, a preliminary raising of the index by means of tuberculin will minimize the risk of dissemination, and a continuation of such treatment after the operation will expedite the cure. It may, however, be noted that cases of this kind, so advanced that even amputation was advocated, have cleared up in such a marvellous manner under tuberculin and the usual therapeutic measures that no case need be considered hopeless until such measures have received trial (see Chart XII., for instance, of such a case).

CHART XII. (Dr. J. W. E.).

SEVERE TUBERCULOUS SYNOVITIS OF KNEE. FIRST FOUR MONTHS OF TREATMENT.



Fluid from joint when inoculated into a guinea-pig produced typical generalized tuberculosis in eight weeks. Complete cure in six months, with perfect mobility of joint.

Secondary infections will, of course, require their appropriate vaccines.

Western (*loc. cit.*) gives his results in twenty-six cases as follows :

Fourteen cases were cured.

Five cases showed marked improvement, and were still under treatment.

Two cases showed slight improvement.

Five cases showed no improvement, but two of these were senile cases in patients over sixty.

In young subjects and early cases cure and good movement may be expected; but where there is much destruction of tissue and sinuses are present, progress is slow and movement may be considerably limited.

Raw[1] records his experience in twenty-seven cases, mostly of a chronic or subacute variety: 'The cases where the best results were obtained were those in which there was some suppuration or sinus leading directly down to tuberculous disease. In cases of pulpy disease of the joints there was, in many instances, marked diminution in the size of the joints with absence of inflammation and more movement.'

Turton treated five cases, one being of the elbow, the other four spinal. The former was completely cured. Of the spinal cases one had had three operations, and there were sinuses in the back, loin, and iliac region. Despite secondary infection with *Staphylococcus albus*, the patient did extremely well, gained two stone in weight, and has been at work for over a year. In the second, an early case, the disease was apparently arrested. The third was an old case, and was only under treatment a short time, when improved general health resulted. The last case was hopeless from the first, and died of lardaceous disease.

Painter[2] reported on eleven cases as follows. He excludes two cases as being unfair. The other nine were

[1] *Lancet*, February 15, 1908, p. 480.

[2] *Boston Medical and Surgical Journal*, October 31, 1907, p. 621.

all advanced cases, usually with mixed infections. Two cases were extraordinarily improved, one considerably so; four not at all. He considers the method worthy of a longer trial, and believes that with a more judicious selection of cases better results would be forthcoming.

In my own experience these cases do extremely well, especially if treatment be simultaneouly directed against any secondary infection; the cases which do not do well are those in which other parts are also affected, where there is marked wasting or signs of lardaceous disease, or where secondary infections cannot be controlled owing to neglect on the part of the patient.

Lupus and Other Tuberculides of the Skin.

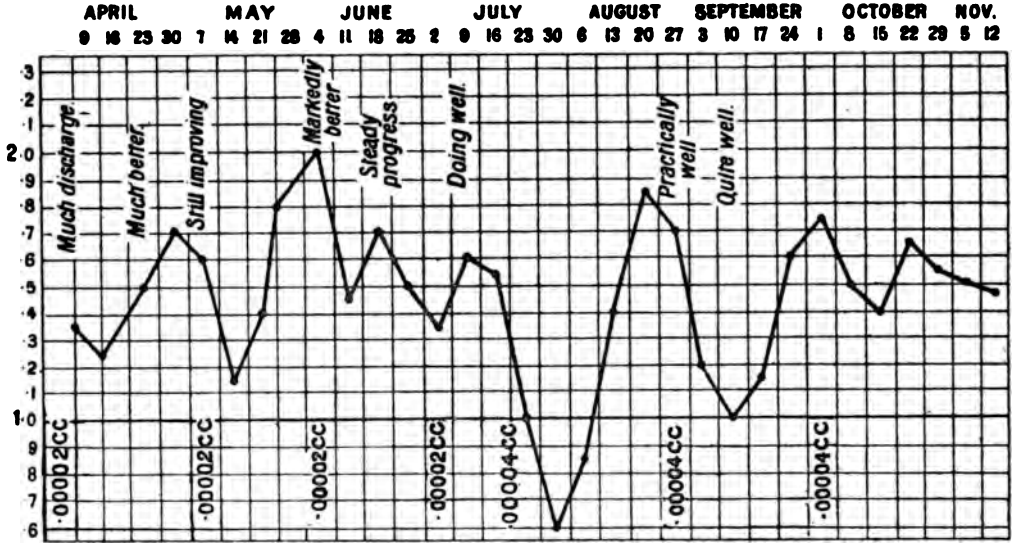
In no other branch of tuberculin therapy have such absolutely discordant results been obtained. Upon the one hand, we have the following opinion of Reyn and Petersen :[1] 'The results of the sole treatment with T.R. have been very bad. We could not in any of the cases see any improvement at all following treatment according to Wright's method. In the most fortunate cases the affection remained stationary; in most of the cases it became worse. We wish especially to call attention to the fact that in two out of the three early cases the disease spread remarkably quickly during the T.R. treatment. We, therefore, feel bound to dissuade practitioners from employing this method as a sole treatment for lupus vulgaris, both in old cases and in fresh apparently benign cases.'

Upon the other hand, Raw :[2] 'Twenty-four cases of lupus have been treated, and it is here that the very

[1] *Lancet*, April 4, 1908, p. 1004. [2] *Ibid.*, p. 481.

CHART XIII.

CASE OF CARIES OF SUPERIOR MAXILLARY BONE. PURE TUBERCULAR INFECTION.



It will be noticed that the injections of 0·00004 c.c. on July 23 and August 27 produced very great fluctuations in the index, indicating that these doses were unnecessarily large. The patient, however, continued to do extremely well, and on September 10 no sign of the injection remained beyond a slight scar. The considerable reaction of index to injection, however, indicated that in all probability tubercle bacilli were still present. Injections of reduced doses were therefore continued until the index remained practically steady.

best results of tuberculin are obtained. All stages of the disease seemed to respond rapidly to injections, and in all the cases in which I have used tuberculin without any other treatment, such as scraping or medication, the ulcerated surface has healed with a firm cicatrix, and in only two instances so far has the disease recurred.'

Between these two diametrically opposed opinions are to be set the experience of Wright and of Bulloch and Western.

Wright finds that in these varieties of lupus where the skin is dry and scaly—so-called lupus psoriasis—tuberculin is of little avail; while in suppurating lupus, where mixed infection by the *Staphylococcus albus* is present, good results can only be achieved by a simultaneous attack upon the secondary infection.

Bulloch and Western also find that the ulcerative type does much the best with tuberculin, especially if combined with fomentations. Treatment may have to be very prolonged, and is best continued long after disease has apparently disappeared, as fall of index seems to predispose to a renewed attack.

Whitfield's results have been disappointing.

Western (*loc. cit.*) records the successful treatment of two cases of erythema induratum, one presenting ulceration, the other not.

Whitfield [1] finds that tuberculous ulcers have done well, even though in some cases the surroundings have been as adverse as possible. Of two cases of Bazin's disease, one apparently completely recovered; the other, after improving enormously at first, relapsed, and seemed to derive little benefit from further treatment.

[1] *Practitioner*, May, 1908, p. 697.

Tuberculosis of the Genito-Urinary System.

Pardoe[1] lays stress upon the frequency and non-recognition of this form of tuberculosis, and especially of that of the bladder. So disappointing have been the results of operative treatment and of all kinds of bladder washes and instillations that he declared that he himself had never met with a case even of apparent cure of vesical tuberculosis by such means. Tuberculin treatment has here met with success that can only be called brilliant. Pardoe himself treated twenty-one cases with tuberculin, many of these before opsonic work was known. Despite this fact, and the certainty, as he himself admits, of having at times given much too large doses and at improper intervals, he obtained the following results :

TABLE XIV.

	Per Cent.		Per Cent.
Cured 5 cases out of 21	24	No improvement in 6 cases out of 21 ..	28
Greatly improved 4 cases out of 21	19	Death in 6 cases out of 21	28
	43		56

He, however, considers that tuberculin should never be given in genito-urinary cases if the orifices of both ureters are infected.

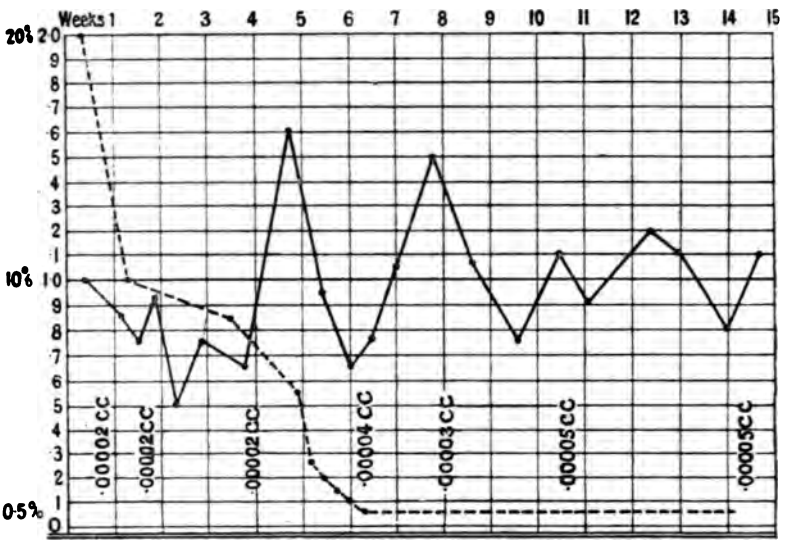
Other observers whose work has been guided by opsonic determinations do not agree with this, and have obtained even more encouraging results (Chart No. XIII., a case under Dr. Eyre, affords an especially good example of this). Thus, Western (*loc. cit.*) says that where adequate treatment has been carried out good results have followed. In one case with slight ulceration of the

[1] *Lancet*, December 16, 1905, p. 1766.

trigone, pain and frequency of micturition with blood and bacilli in the urine, and a hard, nodular prostate, all urinary symptoms disappeared in six months, though the prostatic condition remained.

Turton (*loc. cit.*) treated 4 cases of tuberculous kidney;

CHART XIV. (J. W. E.).



Dotted line = percentage of pus in urine.
Continuous line = tuberculo-opsonic index.

This chart exhibits the first four months' result of treatment in a very bad case of renal and vesical tuberculosis. The cystoscope showed advanced disease of the right kidney, slightly earlier in the left kidney, and advanced in the bladder. The patient improved greatly under treatment, and was alive and in fair health two years from the commencement of treatment.

1 died, the other 3 were greatly improved, and, in Turton's opinion, derived very great benefit from the injections, especially as in 2 of these all the resources of surgery had been exhausted.

Western (*loc. cit.*) records 15 cases of tuberculous

epididymitis. Of these, 6 were cured in from three to nine months; 4 were greatly improved, the sinuses healed, and though the disease was still evident, the patients were able to go about; 4 had only been under treatment less than two months, but were doing well, and 1, which also suffered from diffuse pulmonary phthisis, alone derived no benefit. Western concludes that good results may be expected, even when the disease has broken down and sinuses are present.

The importance of paying due attention in these cases to secondary infections, especially by the *Bacillus coli communis*, can hardly be overestimated.

Tuberculosis of the Intestines.

Very little use appears to have been made of tuberculin therapy in this condition. Turton (*loc. cit.*) records the following remarkable case: 'The abdomen was opened, and such extensive disease found of the cæcum and ileum that removal was impossible. Thirty-eight injections of T.R. and twenty-one of B.C.C. vaccine were given in sixteen months, with the result that the patient gained 16 pounds in weight, and the tumour, which was the size of a goose's egg, entirely disappeared. The patient has been back at work over a year, and has only very rare attacks of pain very mild in character.'

Tuberculous Peritonitis.

Here excellent results have been obtained, both with and without laparotomy. The best procedure appears to be preliminary raising of the index with T.R., laparotomy, and, after allowing the full effects of the auto-inoculation induced by the operation to pass off, resuming tuberculin

treatment. Raw (*loc. cit.*) records his results in eight cases, four being of the dry plastic variety, four associated with fluid in the abdomen. All recovered, and were discharged well after twelve inoculations. He considers that tuberculin is an absolute specific in cases where the disease is confined to the abdomen. Wright[1] gave the following details of a most interesting case : Laparotomy had been performed two months previously, without any resultant improvement. A temperature of 100° F. persisted, the wound discharged, and the condition became desperate. Under T.R. the temperature came down to normal in six weeks, and in three months the patient was discharged. In six months the gain in weight equalled 27 pounds, and six months still later the patient was seemingly perfectly well.

Tuberculous Meningitis.

Even in this extremely grave form of tuberculosis successes have been reported. It is not to be supposed that there have not been failures, but, on the other hand, some successes also have not yet been published.

Buchanan showed before the Liverpool Medical Institute on December 5, 1907, a child who had suffered from tuberculous meningitis, and recovered after an illness of four weeks, with coma for eight days. The symptoms were classical, Calmette's test reacted positively, and the cerebro-spinal fluid contained excess of lymphocytes. An injection of 0·000025 c.c. T.R. was given ; the child showed almost immediate improvement, and gradually regained consciousness. Three weeks later the dose was repeated. Recovery was uninterrupted, and the child was quite intelligent and able to run about.

[1] *Clinical Journal*, November 9, 1904.

Raw (*loc. cit.*) relates the following account of four cases, which exhibited all the classical symptoms : In two, tuberculin had no effect, and the children died; in the other two, all the symptoms disappeared after four injections, and the children made a rapid recovery.

Ocular Tuberculosis.

My experience in this form of tuberculosis, whether of the choroid, iris, or cornea, has been uniformly favourable during the past twelve months—*i.e.*, since my adoption of mixed human and bovine T.R. as the immunizing agent. Cases for which clinical experience would have indicated a course of six or nine months' treatment with human T.R. have recovered instead in four or six. Two cases—one of tuberculous choroid and cornea, the other of episcleritis, with tubercular glands—are making exceptional progress, the improved general condition and increase in weight being also very marked. No other treatment except a little atropine is being employed.

CHAPTER VII

STAPHYLOCOCCAL INFECTIONS

THE *Staphylococcus albus* and *aureus* may be the cause of inflammatory and suppurative processes in various parts of the body. Among acute forms of infection may be instanced Suppurative Periostitis and Osteomyelitis, Ulcerative Endocarditis, Pleurisy, Peritonitis and Meningitis, Carbuncle and Furuncle, Endometritis, and various Pyæmic conditions ; among its chronic manifestations are Acne, Ulcers, and Sycosis. It may also secondarily infect cases due to tubercle, *Bacillus coli communis*, *Bacillus typhosus*, and streptococcus, etc. Its relationship to chronic gleet is discussed under the chapter on the Gonococcus.

ACNE.

The index in these cases is consistently subnormal, varying from 0·2 to 0·8. The isolation of the organism in such cases has already been dealt with, and also the method of preparation of the vaccine. This organism is an especially easy one to deal with in every respect. The response to injection is always marked by such definite clinical reactions that frequent estimations of the index may, as a rule, be dispensed with ; indeed, some venture to do without them altogether. The negative phase is nearly always indicated by a crop of suppurative foci, which, however, abort in a day or two. The appearance of a second crop is the signal for a fresh injection, which

is usually required at intervals of fourteen to twenty-one days. Personally, however, I think it better practice always to do the index the day before a proposed injection. A very suitable dose to commence with is 250,000,000 organisms, except, perhaps, in tropical climates, where, I am advised, initial doses of 100,000,000 are more appropriate. This soon requires increasing to 500,000,000 and 750,000,000, the necessity for this being evidenced by the recurrence of mild attacks. Later larger doses still may be necessary. In the worst case of acne I have ever seen doses of 1,750,000,000 bacteria were given towards the end of treatment at fortnightly intervals, the index then remaining steadily between 0·9 and 1·2, when recovery was soon completed. It is well to note that very slight cases may prove extremely obdurate, especially if the general health of the patient be good and the bowels require no regulation. In one such case—the mildest that I have had under my care—a very confident prognosis was given, with the result that in six months little progress had been made, and cure was only secured by the use of a dosage of 4,000,000,000 at ten days' intervals.

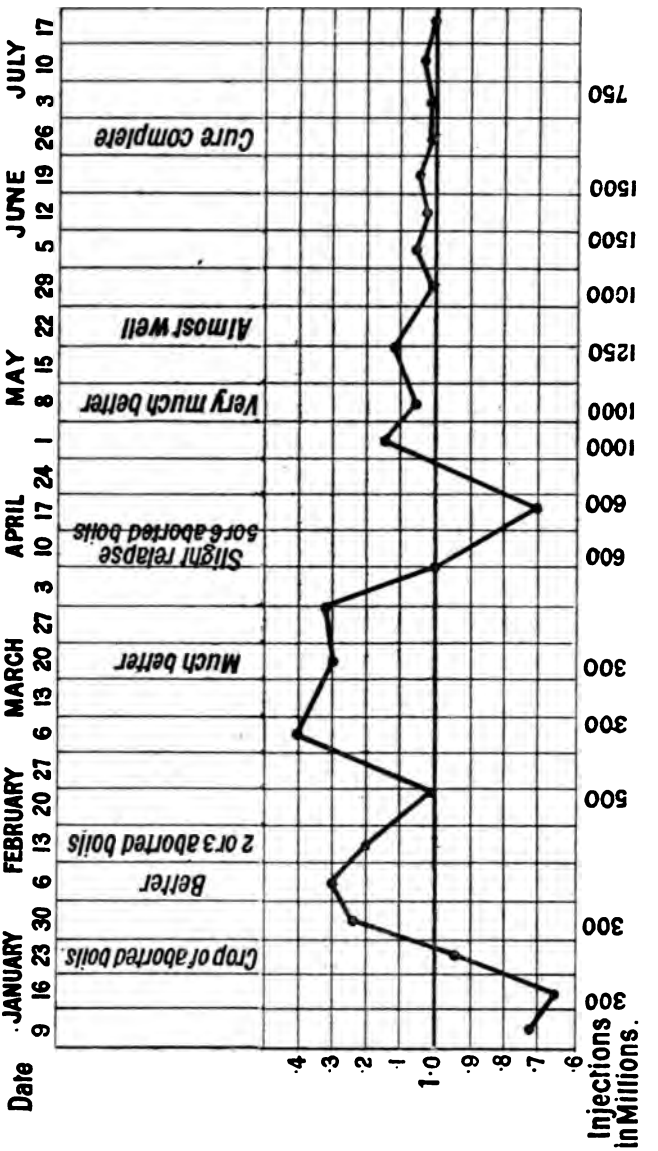
In the case of deep-seated foci which refuse to come to a head—acne indurata—hyperæmia by means of dry-cupping is a very useful adjuvant to the vaccine therapy.

The type of case which yields the least satisfactory results is that characterized by marked oily seborrhœa, abundant comedo, and few suppurative foci. Here especial attention, both local and general, will require to be paid to the seborrhœa and the comedines should be systematically expressed.

Treatment must be persisted in even for six or eight months, until not only do fresh foci fail to appear, but even the old scars have begun to disappear. Diminished

CHART XV.

VERY SEVERE ACNE OF FACE, NECK, SHOULDERS, AND BACK.



doses at prolonged intervals will in most cases complete the cure.

A small percentage of cases remain entirely obdurate, while others relapse after apparent cure. In these latter it is well to supplement a fresh course of vaccine therapy with yeast or iodopin by the mouth or nuclein subcutaneously. As a rule, the best result will be secured by the use of an 'autogenous' vaccine—*i.e.*, one prepared from the patient's own organisms. This especially holds for cases of 'acute indurata.' On the contrary, those from which organisms of but slight virulence and feeble power of growth are obtained do best with a vaccine prepared from a more virulent strain. Most cases will progress very satisfactorily under a polyvalent, stock vaccine.

Boils and Carbuncles.

The results recorded by many observers in boils and carbuncles, of which the greater proportion are due to '*aureus*,' have been uniformly good. Thus, Whitfield[1] says: 'In all the cases of furunculosis which I have treated I have obtained complete, and up to the present durable, success.' Western :[2] 'Nine cases of furunculosis were treated with '*aureus*' vaccine in every instance, with completely satisfactory results. All the cases of carbuncle were ones which, in spite of incision, fomentations, and local antiseptics, showed no adequate attempt at repair or healing, yet all made rapid recovery.' Hartwell and Lee[3] draw the following conclusions from their results in 100 cases of '*aureus*' infections: 'Treatment with vaccines

[1] *Practitioner*, May, 1908, p. 698.

[2] *Lancet*, November 23, 1907, p. 1449.

[3] *Boston Medical and Surgical Journal*, vol. cvii., No. 16, p. 523.

is the most effectual treatment for boils and carbuncles. There is marked diminution in the pain and tenderness. After twenty-four hours there is a profuse discharge, which continues till the focus clears up. With boils about the face, the especial value of the treatment is the prevention of scarring. Although the vaccine treatment does not prevent recurrence, cases of chronic furunculosis can be absolutely controlled by occasional inoculation.' The initial dose is from 100,000,000 to 250,000,000.

Sycosis.

Various factors tend to render the successful treatment of this complaint more difficult than the preceding. The disease is a very chronic one, and results in seriously diminished powers of resistance in the skin, and irritation is kept up by local conditions, such as nasal discharge and dust; the organisms are, moreover, difficult of access for the immunizing lymph. For these reasons relapse is also liable to occur. Depilation by the 'X rays' or other means will considerably aid in the cure, but even then treatment may have to be very prolonged.

Periostitis and Osteomyelitis.

When staphylococci complicate a tubercular infection, as in psoas abscess, fistula '*in ano*,' joint and bone disease, etc., vaccine injections prove of the utmost value to the surgeon. Indeed, I have seen cases which, despite repeated operation, persistently refuse to get well, clear up as if by magic after two or three injections of staphylococcal vaccine as adjuvant to tuberculin. Simple acute infections invariably do well, but long-continued cases, complicated by lardaceous disease, are not nearly so hopeful.

Septicæmic and Pyæmic Cases.

Few such have as yet been recorded. Whyte[1] details the result of a case in a man of fifty-six, with varicose ulcers of the leg and pyrexia, as high as 104°, of three months' duration, with occasional rigors and night-sweats. A pure culture of staphylococcus was obtained from the blood, the index being 1·2. An injection of 250,000,000 was given, with the result that immediate improvement began. Next day the index was 0·7; subsequently it was 1·6, 1·8; and on the eighth day 2·6. Upon the tenth day the blood was sterile, and further treatment was unnecessary.

Turton (*loc. cit.*) records three cases. One of pyæmia originated in a septic osteomyelitis. There was a septic temperature, and multiple abscesses formed almost daily. Three injections of *Staphylococcus aureus* did not seem to have any influence, and the patient died nine days after the first injection.

The second case developed septicæmia a week after parturition. The temperature was 102° F. for five nights. Two injections were given at intervals of forty-eight hours. Twenty-four hours after the second injection the temperature dropped to normal, and recovery was uninterrupted.

The third case was subsequent to miscarriage. The pulse was 130, temperature 104° F., and the condition desperate. Five injections were given at intervals of two to four days. She improved greatly, and eleven days after the first injection temperature was normal. Pulmonary embolism unfortunately supervened, and death resulted twenty days after the commencement of treatment.

[1] *Edinburgh Medical Journal*, December, 1907, p. 555.

Wright[1] also records a very interesting case. The patient suffered from mitral disease, and had had eight months of occasional pyrexia, with pulmonary infarction and cerebral embolism. A staphylococcus of somewhat aberrant characteristics was cultivated from the blood, and an 'autogenous' vaccine prepared. The experience with this was much more favourable than had been that with a stock vaccine previously employed. Six injections—three of 5,000,000 and three of 10,000,000—were given under the guidance of the opsonic index. The temperature soon became normal, and complete recovery ensued.

Very varying dosages have been employed by different observers. Some have used doses as low as 5,000,000, others as high as 1,000,000,000.

In these septicæmic cases the best results can only be expected from the use of an 'autogenous' vaccine, administered under the guidance of the opsonic index. The temperature may come down to normal after a single injection, and subsequent rise may be too late an indication of the necessity for fresh inoculation, while a persistent pyrexia affords no indication as to whether the dosage is inadequate or the patient incapable of an immunizing response.

In cases where index determinations cannot be made it is impossible to do more than suggest an initial dose of 10,000,000, to be increased next day if no fall of temperature result, the increases to be continued and doses given every other day till the temperature does fall or clinical symptoms suggest that the patient is incapable of response. The subsequent course of treatment will be guided by the temperature and clinical condition.

[1] *Lancet*, November 2, 1907, p. 1217.

CHAPTER VIII

THE STREPTOCOCCUS

STREPTOCOCCI, like staphylococci, cause inflammation and suppuration in all parts of the body. Till quite recently reliance was placed upon injections of antistreptococcic serum in such cases as Erysipelas, Pyæmia, Puerperal Fever, Periostitis, and Endocarditis. The frequent failure of this treatment is now explicable owing to the recognition of the fact that the streptococcus is not a single individual, but is a generic name for a large and very heterogeneous class, the members of which are capable of producing the most varied forms of lesion.

Gordon[1] suggested the classification of the streptococci according to the reactions they displaced in the following nine media: Litmus milk, neutral red agar, and broth containing 1 to 2 per cent. of, respectively, saccharose, lactose, raffinose, inulin, salicin, coniferin, and mannite.

Andrews and Horder have extended this work and, combining with these nine tests observations as to growth on gelatine at 20° C. morphology in broth, and pathogenesis towards the mouse, have divided the streptococci into the following types (see Table on page 158).

Other modifications in, and additions to, these tests have been made, but no satisfactory method of classification has yet been devised.

[1] Local Government Board's Reports, 1903-04.

The importance of the bearing that the variety of the bacillus present in any given case of streptococcal infection has upon the choice of a vaccine appropriate to the case is evident.

Horder[1] investigated this question in twenty-eight cases of ulcerative endocarditis, of which eighteen proved to be due to streptococci. The majority of these proved to belong to the 'salivarius,' and 'fæcalis' types, indicating that infection has occurred either via the tonsil or intestine.

TABLE XV.

	S. Pyogenes.	S. Salivarius.	S. Anginosus.	S. Fæcalis.	Pneumococcus.
Milk clot	..	+	+	+	±
Neutral red	..	+	±	±	..
Saccharose	+	+	+	+	+
Lactose	+	+	+	+	+
Raffinose	..	±	..	..	+
Inulin	..	..	..	..	±
Salicin	±	..	..	+	..
Coniferin	..	..	..	+	..
Mannite	..	..	..	+	..
Growth in gelatine at 20° C.	+	±	..	..	..
Morphology in broth ..	longus	brevis	longus	brevis	brevis
Pathogenesis for mouse	+	..	+	..	+

+ = Formation of clot in milk, and acid in other media.

The cases in which the *Streptococcus pyogenes longus* occurs are relatively few, and belong to the fulminant type, being usually rapidly fatal. Why the other cases run such a prolonged course and exhibit so few signs of auto-intoxication, although bacteria may be present in the blood in large numbers, is evident from consideration of this fact, that the infecting organisms are the comparatively non-virulent streptococci of the salivary and intestinal types.

[1] *Practitioner*, May, 1908, p. 715.

Wilson[1] examined the streptococci isolated from five cases of streptococcal meningitis. Two were not fully studied owing to death of the cultures—of these, one was probably pneumococcus; the other was not 'fæcalis,' but possibly 'pyogenes longus.' The other three appeared to belong to the 'fæcalis' variety.

Streptococcal Septicæmia and Pyæmia.

Several cases have now been recorded in which vaccine therapy by means of an autogenous vaccine has been resorted to in this variety of systemic infection. The first case was described by Sir James Barr before the Liverpool Medical Institute on May 3, 1906, the treatment having been conducted by Captain Douglas. It was a very severe case, rigors occurring every twenty-four hours or oftener, when the temperature mounted to 104° or 105° F., and was followed by profuse sweating. There was an attack of pleurisy with pleuro-pericardial friction, but without marked effusion. All the various brands of anti-streptococcal serum had been tried without much benefit.

Douglas isolated the streptococcus from the patient's blood, and a vaccine was made. The index was estimated twice daily, and injections given of 5,000,000 to 12,000,000 cocci at each fall of the index.

The patient made an excellent recovery, and, except for the effects of phlebitis in the left lower limb, was soon quite well.

Sutcliffe and Bayly[2] have described a case of streptococcal septicæmia in a boy of fourteen, who had been

[1] *Lancet*, December 28, 1907, p. 1816.
[2] *Ibid.*, August 10, 1907, p. 367.

operated on for discharging tubercular glands, which was successfully treated with a streptococcal vaccine. Pus was found along the track of the right deep femoral vein, and there was threatened formation in a similar situation in the left thigh. The cocci were isolated from the blood, and the index found to be 0·66. An injection of 10,000,000 organisms raised the index to 1·15 by the following day. In the course of forty-five days ten injections, varying in amount between 10,000,000 and 50,000,000 organisms, were given. Reduction of temperature, elevation of the index, and general improvement in the patient's condition ensued after each injection, and complete recovery was the ultimate result. Upon two occasions, when manipulation of the limb was performed, considerable depression of the index, due to auto-inoculation, was observed the next day.

Turton (*loc. cit.*) has had experience of three cases.

The first had received a scratch from a dirty wire, there was œdema and redness of the hand and arm, and great prostration with a temperature of 102° F. Injections were given upon the third, fifth, eighth, and twelfth days after infection, and an excellent recovery ensued.

Case number two, also of septicæmia, had a favourable issue after four injections spread over seven days.

The third was one of puerperal septicæmia, which seemed hopeless from the first. Two injections on the ninth and eleventh days after parturition seemed to produce no good result.

Crowe and Wynn[1] give the following interesting account of a case of puerperal septicæmia due to mixed infection by streptococcus and *Bacillus coli communis*, and therefore of bad prognosis. Upon the ninth day after labour the temperature rose to 99·6° F., and clots came away; on

[1] *British Medical Journal*, August 8, 1908, p. 303.

the fifteenth, sixteenth, and seventeenth days the temperature rose to 100·4° F., and upon the eighteenth to 101° F., when *Streptococcus pyogenes longus* and *Bacillus coli communis* were isolated. Upon the eighteenth, twentieth, twenty-first, twenty-second, and twenty-fifth days 10 c.c. of antistreptococcal serum were given without any good result. On the twentieth day the index to *Streptococcus pyogenes* = 0·65. Upon the twenty-fifth day 70,000,000 of *Bacillus coli communis* and 10,000,000 of streptococcus of autogenous vaccines were given. In the evening the temperature rose to 102° F., but on the third morning it fell to normal, the indices being then to *Bacillus coli communis* 1·58, to streptococcus 1·72. The temperature remained normal for four days, then rose to 100° F. This was recognized as being due to two carious teeth, with abcesses at their roots. These were extracted, and recovery proceeded uninterruptedly.

Wright[1] relates his experiences in six cases of streptococcal septicæmia (one of these being the case of Barr and Douglas, already described). Of these, two cases were cured, having made very satisfactory immunizing responses; another made a very good response, but died from cardiac complications four days after defervescence. Three cases died without making any immunizing response to the inoculations, despite the use of doses varying greatly in magnitude.

Results such as those recorded above, in a complaint of such grave prognosis as streptococcal septicæmia, can only be described as highly satisfactory. Control of the inoculations by means of the opsonic index is highly desirable, and failure to secure an immunizing response indicates extreme gravity of the case.

[1] *Lancet*, August 24, 1907.

Should it be impossible to make determinations of the index, the temperature-chart and clinical condition of the patient must be taken as the guide for repetition or increase of the initial dose of 5,000,000 to 10,000,000.

In erysipelas, empyema (of which 55 per cent. in adults and 15 per cent. in children Netter has shown to be due to streptococci), secondary joint infections, dacryocystitis, ulcers, and infected wounds and endometritis, the *Streptococcus pyogenes longus* is, as a rule, the variety present. Initial doses of 25,000,000 to 50,000,000 may safely be employed, and a completely satisfactory result may be anticipated.

Erysipelas.

Schorer[1] studied the index in erysipelas, and the effects of therapeutic inoculation by vaccines and, came to the following conclusions :

The onset of an attack causes rise of index, which attains a maximum about the third day, and then gradually falls.

No constant change in index occurs at the time of desquamation, and only half the patients discharged as cured have a higher index on discharge than they had on admission.

Injections of 25,000,000 millions cause a rise of index after twenty-four hours without any preceding negative phase. Next day there is a slight fall, but a raised index is maintained for about seven days. With a dose of 50,000,000 the rise is delayed till the second day.

Inoculation does not prevent migration or recurrence, but seems to shorten the duration of an attack by about three days.

[1] *American Journal of Medical Science*, November, 1907, p. 728.

The index is so variable that it is of no use as an indication of the severity of the disease, nor is it of value in prognosis. No relation was observed between elevation of index and improvement of the patient as the effect of injection. Other observers have obtained much more favourable results, and a case by Butler Harris[1] may be specially mentioned.

From a case of severe facial erysipelas an autogenous vaccine was prepared and administered upon the sixth day when the temperature was 105·4° F., the pulse 140, respiration 45, and the patient in imminent peril. Recovery resulted by crisis, the temperature dropping to 98·8° F. fourteen hours after inoculation.

Wynn[2] also records the following two cases. The first, a medical man, infected his finger at a post-mortem upon a case of ulcerative endocarditis. The infection quickly spread from the finger to the axillary glands and subcutaneous tissue of the arm. Severe erysipelas extended all over the trunk and down the thighs, and the patient became dangerously ill. From the *Streptococcus longus* isolated a vaccine was prepared. The opsonic index rose considerably after the first inoculation, and other inoculations were given, when daily estimations showed the index to be falling. Good response followed each administration. Prior to the first injection, which was given upon the sixteenth day, the temperature had showed daily rises to 102° and 103° F., and on the thirteenth day to 105° F. Subsequent inoculations were given on the eighteenth, twenty-first, and twenty-seventh days. Upon the twenty fourth day the temperature fell to normal, and the patient made a good recovery.

[1] *Practitioner*, May, 1908, p. 647.

[2] *Birmingham Medical Review*, June, 1908

The second case was one of severe facial erysipelas. The temperature showed daily rises to 104° F., and once to 106° F., with remissions to 100° and 101° F. Inoculations of 10,000,000 were given on the third, fifth, tenth, thirteenth, and fourteenth days of the disease. The temperature dropped by crisis on the day following the last inoculation.

Rheumatism and Chorea.

Poynton and Paine have described a form of streptococcus as being the probable causative agent in acute rheumatism. It exhibits no definite distinctive reactions. It is a very small diplococcus, growing best in a mixture of equal parts of milk and broth. It has strong acid-forming tendencies, fermenting glucose, lævulose, galactose, maltose, arabinose, dextrin, saccharose, lactose, salicin, and mannite, but not inulin, dulcite, or sorbite. It turns milk acid, but does not as a rule form a clot. It forms acid in bile salt lactose broth, precipitating the litmus and bile salts. When grown in broth, it forms considerable quantities of formic acid (Ainley Walker); if the broth be then filtered through a porous porcelain candle, the *Streptococcus rheumaticus* will fail to grow in the filtrate, while other forms of streptococcus will grow well. The identity of this organism is still, however, disputed.

The Index to 'Streptococcus Rheumaticus' in Acute Rheumatism and Chorea.

Fordyce[1] observed the index in one case of acute rheumatism with pyrexia, painful, and swollen joints, acute pericarditis and albuminuria. Two days after admission

[1] 'International Clinics' (eighteenth series), vol. i., p. 40.

the index = 0·59. During this day the fever and the physical signs of pericarditis subsided. Next day the patient was markedly better and the index = 1·1 ; for the heated serum it was 0·45 as compared with 0·1 for a heated normal serum. The patient steadily improved, and six days after admission the index = 1·3.

In ten cases of chorea he found the index, as a rule, low upon admission, rising later as the general health improved.

The lowest index found = 0·6, the highest 1·8. Upon several occasions the index was normal, and all such indices occurred when improvement in the clinical symptoms was taking place, and upon more than one occasion was an intermediate step from a low to a high index.

Streptococci in Scarlet Fever.

The view has steadily grown in favour of late that streptococci are intimately connected, at all events with the complications of scarlet fever, if not with the pathogenesis of the fever itself. Thus, in over 70 per cent. of cases with albuminuria, streptococci are copiously voided in the urine, and in about 15 per cent. of cases without albuminuria. Bearing this in mind, Banks [1] has studied the variations in the opsonic index of the blood to streptococci as the disease progressed. He found that in cases running a fairly normal course the opsonic power towards streptococci varies in a pretty definite and constant way. It is decreased during the early febrile period, and rises to normal or above normal during the defervescence and general decline of symptoms. It falls during the second and third weeks, and even in uncomplicated cases the

[1] *Journal of Pathology and Bacteriology*, October, 1907, p. 113.

index may be comparatively low. There is an increase to normal or over during the fourth and fifth weeks. In fatal cases with severe angina the opsonic power is markedly subnormal. Complications alter the usual curve, causing both absolute and relative differences. Thus, the opsonic power is decreased at the onset and during the earlier period of albuminuria and secondary adenitis ; as convalescence is established the index rises. The opsonic values do not furnish many data for prognosis, but, in general, a persistent low index during nephritis or other serious complication is an unfavourable sign.

The author, therefore, thought it worth an effort to determine whether the course of scarlet fever could be favourably influenced by the administration of a vaccine prepared from the streptococci isolated from the throats of scarlet fever patients. From the throats of each of twelve such cases the *Streptococcus* '*conglomeratus*,' both of the small and large types, was recovered, and with great difficulty a mixed vaccine was prepared. The effect of this was then tested, in conjunction with Dr. Goodall, in six cases of uncomplicated scarlet fever, but apparently without producing the slightest good effect, doses varying from 10,000,000 to 50,000,000 were employed. This result, although discouraging, is, of course, not conclusive, and it is quite possible that good may be effected in cases complicated by angina, adenitis, and nephritis, as there is little doubt of the streptococcal nature of these complications.

CHAPTER IX

THE PNEUMOCOCCUS

THE pneumococcus causes a great variety of suppurative conditions, among which are Pneumonia, Pleurisy, Pericarditis, Endocarditis, Empyema—both pulmonary (according to Netter, 15 per cent. of adult secondary cases and 65 to 90 per cent. of all cases in children) and of the accessory air sinuses—Peritonitis, Otitis, Meningitis, Conjunctivitis, Arthritis, Periostitis, Nephritis and Perinephritis, Metritis and Pyosalpinx, Abscesses, and Pyæmia. It is also the cause of chronic Ulcus Serpens Corneæ.

PNEUMONIA.

MacDonald[1] studied the index in eight cases of pneumonia, and found that while the temperature is rising and during the fastigium the opsonic index is below normal, whereas at the onset of the crisis there is a sudden rise, even as high as 1·6.

Subsequent observations have shown that in very severe cases failure of the index to rise in this manner at the crisis is a matter of very grave importance, and that such cases usually die.

Recent attempts have been made in America to treat pneumonia as a routine by injection of a vaccine, and considerable success has been claimed. The temperature

[1] Pathological Society, London, January 17, 1905.

is said to fall several degrees within twenty-four hours; the crisis is precipitated within three or four days, and the convalescence is rapid and complete. The whole duration of the disease when so treated is claimed to lie within a fortnight.

Butler Harris[1] refers to four cases of pneumonia which failed to immunize themselves, and responded at once to the introduction of a vaccine made from the patient's own pneumococcus—details of the cases are not given. Favourable experiences of the routine injection by 25,000,000 organisms of cases of acute pneumonia have been communicated to me privately, but have not as yet been published.

Unresolved pneumonia would appear to be particularly suitable for vaccine therapy.

Coleman recorded before the Royal Academy of Medicine, Ireland, on March 2, 1906, such a case treated by inoculation of pneumococcal vaccine with very satisfactory results.

On the thirty-eighth day of attack the pneumococcic index was 0·6; 46,500,000 cocci were therefore given. There was no disturbance, local or general. Next day the index was 0·69, and the physical signs were those of pneumonia of five or six days' standing.

6 days after injection the index = 1·17, and the patient was much better.
10 days after injection the index = 0·89, and 46,500,000 were again given.
3 days after second injection the index = 1·13.

Eleven days after the second injection the patient was in excellent health, and for six weeks subsequently the index was observed to be slightly over normal.

[1] *Practitioner*, May, 1908, p. 647.

Briscoe and Williams[1] subjected four such cases, which were not improving under ordinary treatment, to vaccine therapy. Cultures were made from the patients' own organisms, and the guidance of the opsonic index was utilized.

Case 1 was in a child aged one and a half years. A month after admission a consolidation at the right base was still unresolved. The index being 0·9, an injection of 20,000,000 cocci was given. A slight rise of temperature resulted, and the child was not so well for eighteen hours. He then began to improve in weight and general condition.

2 days after the first injection the index = 1·2.
4 days after the first injection there were only a few crepitations and slight bronchial breathing.
5 days after the first injection the index = 1·3.
6 days after the first injection there were crepitations, but no bronchial breathing.
9 days after the first injection the index = 1·2.
11 days after the first injection 10,000,000 cocci were given without any ill effect, and next day index = 1·4.
2 days after the second injection crepitations were audible only at lower and posterior aspect of the lobe.
5 days after the second injection 10,000,000 cocci were given, and next day the chest was clear.

Case 2 was in a child aged one year and nine months, and was readmitted two months after having been admitted for right basal and later apical consolidation. Turbid fluid was found, and one injection of 20,000,000 given. The child steadily got worse, and died in a few days. Post-mortem, loculated septic pericarditis with universal mediastinitis, collapse and consolidation of the right lung was found. The presence of the old-standing septic pericarditis may be held to have contra-indicated vaccine therapy, and the case is hardly a fair one upon which to base any conclusion.

[1] *Practitioner*, May, 1908, p. 675.

Case 3 was in a child of two, in whom the temperature remained intermittent after drainage of an empyema. Two injections, the first of 10,000,000, the second of 40,000,000, eight days after the first, were given. Measles, unfortunately, complicated the case, but the authors state that the child's general condition was improved, and the temperature slightly reduced as a result of the inoculations.

Case 4 was one of right basal consolidation with a history of one week in a man of forty-four. Although the temperature soon fell to normal, the local signs failed to clear up. Sixty million organisms were therefore injected on about the twenty-second day, and again thirteen days later. After the first injection the moist sounds cleared up entirely in the next three days, and the sputum diminished two days after the second injection. There was no bronchial breathing, but the breath sounds were a little harsh. His general and mental condition, previously bad, improved rapidly.

The authors' conclusions are that 'in these more or less acute cases the improvement in general condition is quite a marked feature, and it appears to be an important factor in the question of continuing the treatment. The injection produces a stimulating effect, and the patients always seem to be more cheerful afterwards. An increase of weight occurs rapidly in the case of children.'

They also produced decided improvement in two cases of a chronic nature in adults, the history in each dating back ten months. Doses of 50,000,000 and 100,000,000 were employed.

In empyemata good results may be anticipated when vaccine therapy is directed against the organisms found to be present. In only a certain percentage are pneumococci alone present; in some cases they are absent alto-

gether ; in most there is a mixed infection with streptococci, staphylococci, *Bacillus pyocyaneus*, *Bacillus coli communis*, etc. ; and in these a mixed vaccine will have to be employed in conjunction with such measures as surgical experience indicates. Improvement may be slow, and prolonged treatment necessary.

A number of cases have now been reported in which the pneumococcus has been found to be responsible for metritis and pyosalpinx, and in a few instances for a resultant peritonitis and systemic infection. The possibility of this might well be borne in mind by obstetricians and abdominal surgeons, and recourse made to vaccine therapy. Jowers[1] records such a case in a girl of fourteen, in whom a diagnosis of general peritonitis, secondary, probably, to perforated appendix, was made. At operation the appendix was found to be normal, but the right Fallopian tube distended, the ovary swollen and adherent to the pelvic wall. The abdomen contained colourless pus. The pneumococcus was isolated in pure culture and a vaccine made.

Upon the eighth day after operation 50,000,000 cocci were given ; upon the tenth day 60,000,000, and upon the thirteenth day after operation 200,000,000 were given without the control of the opsonic index.

The temperature only came to normal after five weeks, the pulse all this time being high. The child then made a good recovery. The impression conveyed from the published account is that, if the vaccine therapy had been controlled by index determination and persisted in, a more speedy result would have been obtained.

For *Ulcus serpens cornea* and *Pneumococcal conjunctivitis*, see Chapter XIV.

[1] *Practitioner*, September, 1908.

CHAPTER X

THE GONOCOCCUS

THE chief conditions set up by this organism are Urethritis, Periurethritis, Prostatitis, Vesiculitis, Cystitis, Epididymitis and Orchitis, Endometritis, Salpingitis, Peritonitis, Conjunctivitis, Endocarditis, Arthritis, and even Pleurisy and Septicæmia. In these connections a very wide field of utility is afforded, both in the diagnosis and treatment.

THE OPSONIC INDEX IN GONOCOCCAL INFECTIONS, AND ITS UTILITY IN DIAGNOSIS AND TREATMENT.

In acute gonorrhœal infections of the urethra the index, as a rule, first falls for a few days to 0·6 or 0·7; it may then either rise steadily to 1·3 or 1·6, such cases usually doing well under routine treatment, or it may continue subnormal, when they usually pass on into a chronic intractable gleet.

In chronic cases the index is usually low, even 0·3; it is, however, sometimes normal or above normal, but in these cases cocci, as a rule, are to be found copiously in the secretions from suppurating Littré's glands or sinuses, which may continue thus to discharge at intervals for many years.

In acute gonorrhœal conjunctivitis in adults the index may be as high as 2, or even 2·5.

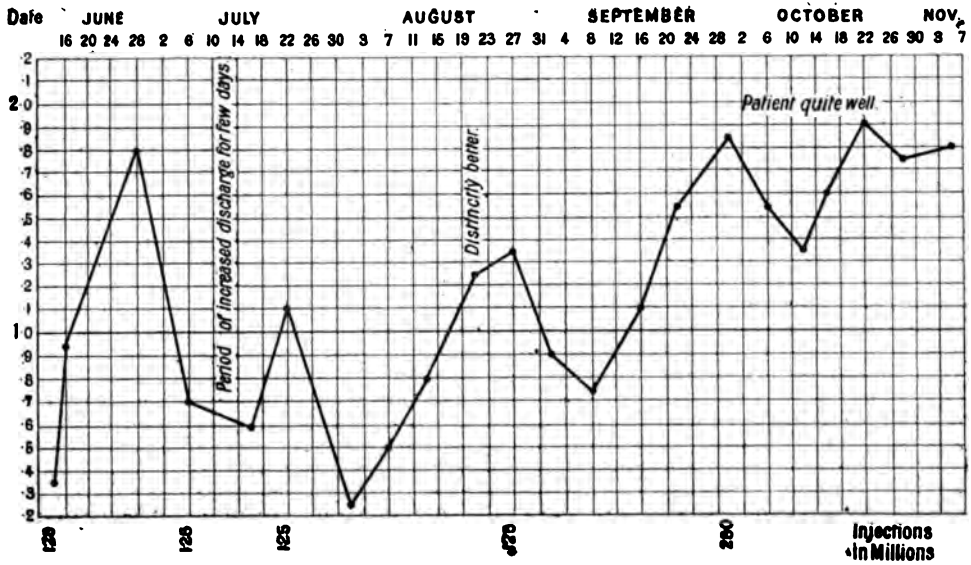
Every genito-urinary surgeon and obstetrician is familiar with the great difficulty of deciding whether an old gonorrhœal infection has disappeared, or of arriving at a diagnosis in cases where a history of an acute attack is not obtainable. In the male it is no very uncommon thing for a discharge to persist even for ten years after an attack of acute gonorrhœa. Stained films do not reveal the presence of any gonococci, but only of streptococci, staphylococci, the bacillus of Friedländer, the *Micrococcus catarrhalis*, and other + and − Gram organisms. The difficulty of advising as to the safety or otherwise of marriage in these cases is considerable. In deciding whether there are any latent gonococci encapsuled in the numerous urethral crypts and diverticula I have found the opsonic index of the utmost assistance. Brief references to a few cases will illustrate this.

Case 1 had a chronic discharge for ten years. No gonococci could be found in films, but the bacillus of Friedländer was present in vast numbers in a state of purity.

The gonococcal index was 1·1, that towards the bacillus of Friedländer 0·6. Non-gonococcal infection was diagnosed, and treatment by means of a vaccine prepared from the pneumobacillus carried out with complete success.

Case 2 was one of twelve years' standing, which had proved obdurate to every form of treatment. No gonococci could be detected in smears or cultures, and the index was 1·2. The patient desired a course of injections with gonococcal vaccine, and five were accordingly given, but, as anticipated, without influencing the discharge. A combined vaccine was then prepared from the urethral

CHART XVI.—Case of Chronic Gleet, exhibiting Prolonged Negative Phases.



This case was one of chronic gleet of seven years' standing. Slight exacerbations were frequent. The chart presents several points of interest. The Gonococcic index was very low—0·35—indicating exhaustion of the protective mechanism. Despite this, splendid response was made to the first injection, the index rising in fourteen days to 1·8, to fall as rapidly to 0·7. The second injection, of like amount to the first, produced a much less satisfactory result, the index being yet lower after ten days; upon the sixteenth day it had recovered to 1·1. A third injection was then given. Upon the tenth day the index had fallen to 0·25, but during this interval the clinical symptoms had altered little. The index then began to rise rapidly, and continued to do so for twenty-six days; as the limit of rise seemed about reached, a fourth injection was then given of 125,000,000 organisms. Study of the curve between the third and fourth injections shows clearly that the third was given prematurely. The rise after the first injection and the subsequent fall were both so rapid that I wished to avoid a similar fall after the second injection; hence the mistake, which was avoided subsequently.

organisms present ; two injections sufficed to reduce these greatly in numbers and variety, and a fresh vaccine was then made.

Two injections with this resulted in great diminution of the discharge, which contained only epithelial and lymphoid cells and few organisms, which were contained within the epithelial cells, and proved very difficult to cultivate. Subsequent irrigation for a few days with weak solutions of perchloride of mercury completely cured the discharge.

In these two cases, then, the gonococcal index was normal, and the diagnosis of non-gonococcal infection was amply confirmed by the results of treatment.

Cases 3 and 4 were each of ten years' standing, and had undergone the most expert surgical treatment, both in England and upon the Continent, but without avail ; exacerbations appeared from time to time without any obvious cause. In Case 3 no gonococci were to be found, in Case 4 only at intervals. The indices were found to be 0·4 and 0·5 respectively ; gonococcal infection was therefore diagnosed, and opsonic treatment advised, with complete success, two injections sufficing in the instance of Case 4.

Case 5 was sent me by Mr. Wyndham Powell, and is peculiarly interesting. The attack was a first one. Intercourse, which had taken place seven days previously, was followed by discharge three days later. The patient at once saw Professor Janet, who diagnosed a simple non-gonococcal urethritis. Mr. Powell was of the same opinion, but, owing to the extensive involvement of Littré's glands, desired confirmation. Cultures of the secretion gave pure *Staphylococcus albus*, even after thorough irrigation of the urethra. The gonococcal index

was found to be 0·9. The staphylococcal index was found to be 0·7. Confirmation was thus afforded of the non-gonococcal nature of the infection, which was considered to be staphylococcal in nature. A vaccine was made, and an injection of 150,000,000 organisms given. A second similar injection was given three weeks later, and the patient appeared to be improving. Unfortunately, he left England a fortnight later, and the success or otherwise of the treatment could not be determined.

Case 6 was a case of old gonococcal infection in the female, the discharge recurring at practically every menstrual period. Advantage was taken of the fact that during a period the index towards any infecting organism falls considerably: two days prior to menstruation the index was found to be 0·7; upon the fourth day it was only 0·3. The diagnosis of gonococcal infection was therefore made, and amply confirmed by the results of opsonic treatment. In three months the woman felt a totally different person, and had gained a stone in weight.

The evidence afforded by these and numerous other cases of chronic urethritis serves to indicate that in many instances, though the gonococcal infection has died out, the gonococcal toxins and antiseptics faultily applied have resulted in a weakened mucous surface, upon which numerous pathogenic organisms, usually of low virulence, are enabled to flourish and multiply. These prove extremely resistant in many instances to local forms of treatment, but sometimes readily respond to injections of vaccines, a series of which may, however, be required. In view of the extreme importance of eliminating every chance of the continuance of a gonococcal infection, it is good practice in all cases where the index is on the borderline of the normal—*i.e.*, 0·8 or 1·2—to begin the treatment

of such cases with injections of a gonococcal vaccine, even though no gonococci are to be found in the secretion. A first dose of 75,000,000 organisms is best given ; should this produce no effect, it may be followed by a second of double the amount. Should only slight disturbance of the index result, the non-gonococcal nature of the infection may be considered established, and treatment then begun with a combined vaccine. Such treatment can do no possible harm, and may prevent a gonococcal case being missed. It must, however, be noted that even persistent treatment of some cases of chronic urethritis will fail to cure entirely the discharge and threads in the urine. The patients feel better, suffer no discomfort and put on weight, yet a small bead of discharge may be expressed in the morning. Although such cases may safely be left in such a condition, none having retrogressed within my experience, further improvement may possibly be secured according to the method I employed in two instances. Both were very old chronic cases, one of thirteen years', the other of fifteen years' standing, and both when they came under my care had profuse discharge which worried them greatly. Every conceivable method of surgical treatment had been employed upon them. After a preliminary course of gonococcal vaccine, a whole series of vaccines prepared from the urethral organisms was employed in turn. Both cases improved very greatly, yet each morning it was possible to express a bead of discharge containing great numbers of organisms, both staining and failing to stain by Gram's method.

As a last resort I decided to inject cultures of living lactic acid bacteria into the urethra, with the aid of an ordinary syringe, twice daily for a week. The first day there was slightly increased discharge and considerable

itching; subsequently the injections resulted in less discharge, but the irritation continued. At the end of a week of this treatment the urethra was thoroughly flushed out with weak potassium permanganate solution night and morning. Next day the irritation had disappeared, and smears were obtained with great difficulty; no organisms could be detected, and cultures were also sterile. Both patients have remained well.[1]

I have of late made a routine practice of giving every case of acute gonorrhœa one or two injections of vaccine, the first being administered as soon as the acuter symptoms have begun to subside, and the thick discharge to diminish. Convalescence has been complete in two or three weeks, and secondary complications and backward extension have failed to appear in any of the series. This procedure can be warmly recommended.

Gonococcal Arthritis.

Cole and Meakins[2] record their observations upon fifteen cases.

They found the index subnormal, varying between 0·2 and 0·7. An initial dose of 200,000,000 to 300,000,000 was found to raise the index above normal in each case, the maximum height being attained between the second and seventh day, while a return to normal occurred on about the tenth day.

The injections were carried out under the guidance of the index (as estimated upon counts of fifty cells), and

[1] The fluid employed for injection can be obtained from W. H. Martindale under the name of 'Trilactine liquid, special, for injection.'

[2] *Bulletin of Johns Hopkins Hospital*, June and July, 1907, p. 223.

gradually raised till 1,000,000,000 were administered. General constitutional disturbance was very rare, and in only one case severe. The interval between injection was seven to ten days. They found that any coincident urethritis or prostatitis was much less amenable to the vaccine therapy than the arthritic condition. In regard to this latter they concluded that the results in the chronic cases were more marked than in the acute ; cases which had progressed but very slowly under other methods of treatment showed much more rapid improvement. Their opinion was that the vaccine treatment had been of distinct value, a conclusion amply borne out by the clinical details given.

Irons [1] has also studied 40 cases of gonococcal infection, 31 being arthritic. In 15 of the cases the index was systematically studied, and found initially to be low, but clinical symptoms were used as the guide to size and interval of injections. The vaccines used were heterologous, and univalent, divalent, or trivalent, little advantage being noticed from the use of a polyvalent vaccine. At first initial doses of 20,000,000 to 50,000,000 were employed, but in later cases these were increased advantageously to 100,000,000 and even 1,000,000,000, the intervals between injections varying from three to seven days. The injection of 500,000,000 dead gonococci into the tissues of a person free from gonococcal infection was found in eight cases to produce practically no constitutional disturbance ; quite otherwise was the result in infected cases. In these, within twenty-four hours, and corresponding to the negative phase, there is increased articular pain, tenderness, rise in temperature, and general malaise, so that the suggestion was made to employ

[1] *Archives of Internal Medicine*, vol. i., No. 4, p. 433.

this reaction as a diagnostic in cases of doubtful gonococcal infection.

Inasmuch as the clinical course of gonococcal infections is very variable, and the great majority of arthritic cases ultimately recover spontaneously, Irons is particularly guarded in drawing conclusions from the results of his observations, but considers that in certain cases of gonococcal arthritis recovery can be hastened by vaccine therapy, this assistance being more marked in subacute and chronic ambulatory cases than in acute ones, although in several such cases improvement was apparently more rapid immediately following an injection than it was before.

Gonorrhœal Vulvo-Vaginitis in Children.

Butler and Long [1] studied the effect of vaccine therapy in twelve such cases. They controlled their work by means of index determination, and reinjected before the index fell again below normal. They found that the dosage could only be determined by investigating each individual case, either a too small or a too large dose resulting in little or no response. The doses varied from 1,000,000 to 50,000,000, and an initial one of 5,000,000 is recommended.

The ages of the twelve cases were between one and a half and twelve years, and the results were compared with those obtained in twelve other similar cases treated locally with potassium permanganate and argyrol.

In four of the twelve cases treated with vaccine clinical evidences of gonorrhœa disappeared in from ten to twenty-one days, and gonococci could not be found in smears.

[1] *Journal of American Medical Association*, March 7, 1908, p. 744.

In five cases a cessation of discharge and disappearance of gonococci from the smears were secured after several weeks of treatment, a change from a univalent to a polyvalent vaccine being found beneficial.

Of the remaining three cases, in two the discharge ceased, but recurred after treatment was stopped, although ultimately gonococci disappeared from smears; in the last case, recurrence was followed by cure.

Of the 12 control cases, in 9 treated respectively twenty-five, twenty-six, twenty-six, twenty-seven, twenty-nine, forty, forty-nine, sixty-three, and ninety-six days cessation of discharge was not secured, while in the remaining 3, under treatment respectively thirty-one, thirty-two, and one hundred and seventy-six days, a favourable result was secured.

Their conclusion is that vaccine therapy appears to be far more efficient, and at the same time scientifically more tenable than local antiseptic treatment in these cases.

Despite the researches of Torrey,[1] who, from a study of the agglutinins and precipitins in anti-gonococcal sera, came to the conclusion that the family gonococcus is heterogeneous rather than homogeneous, the view of its being a definite entity is usually held. Wherever possible, it is undoubtedly best to prepare a vaccine from the patient's own organisms; but should the virulence of these have been reduced by antiseptic treatment or by the long duration of the infection, it is decidedly better to employ a vaccine made from a strain of known high virulence. In eye cases one should inject immediately the diagnosis is established, without waiting to determine the index or prepare a vaccine. The index in all eye infections, acute or chronic, due to whatever organism,

[1] *Journal of Medical Research*, Boston, May, 1907, p. 329.

is, as a rule, exceptionally high. The reason for this is fairly obvious. The circulation of that part is poor, the area of infection small; consequently the toxins formed are absorbed in such minute quantities that they act like very small doses of vaccine, and tend to raise the index. If other areas in the body are infected, as is often the case in tubercular cases, this reasoning does not apply, and the index corresponds to the nature of the other area of infection. That the already high index so often fails to effect cure in these cases is due to the same cause—poor blood-supply and poor lymph flow; hence in such cases high index is no contra-indication to injection.

The dosage in gonococcal cases requires particular attention. Owing possibly to the powerful toxins formed by this organism, the initial doses employed are smaller than in the case of most other organisms: 50,000,000 organisms may be used with advantage upon the first occasion, 100,000,000 being employed upon the second, if indicated by the index. Subsequently larger doses than 500,000,000 are not often required.

As regards the frequency of administration, this should always be controlled by determinations of the index. A negative phase, lasting for a fortnight, with a dose of 100,000,000 or 150,000,000 organisms, is by no means infrequent, in which case little advantage can accrue from fresh injection before the end of a month.

As in the case of tubercle, it is particularly bad practice to inject without estimating the index the day before; if this cannot be done, it is better to err on the side of waiting a week too long rather than on that of injecting a week too soon. It may, however, be noted that occasionally the result of a first injection is a continued negative phase; the index drops a few decimal points,

and is only raised by a second injection of like strength. Should, however, the index still remain depressed, it is best to wait four or five weeks, and begin again with reduced dosage.

Another peculiarity about this organism is the marked improvement of clinical features which occasionally results during the negative phase. Increased discharge often occurs during the first two or three days, but then rapidly diminishes, despite the continued presence of the negative phase. Clinical symptoms are therefore a totally unreliable guide as to the appropriate time for fresh injections.

CHAPTER XI

THE OPSONIC TREATMENT OF CATARRH, NASAL AND TRACHEAL, AND OF THE ACCESSORY AIR SINUSES

DURING the last four years the author has been working continuously upon this question. A paper is appearing upon the subject in the *Lancet* shortly, but some of its essential features may here be given.

THE BACTERIOLOGY.

1. *Of Nasal Catarrh.*—Forty-two cases of nasal catarrh, acute and chronic, were examined bacteriologically and the causative organisms determined, with the following results:

The bacillus of Friedländer alone in 8 cases	= 19·0	per cent.
The *Bacillus influenzæ* alone in 1 case	= 2·4	,,
The *Bacillus septus* alone in 11 cases	= 26·2	,,
The *Micrococcus catarrhalis* alone in 12 cases	= 28·6	,,
The bacillus of Friedländer + *Bacillus septus* in 3 cases	= 7·1	,,
The bacillus of Friedländer + *Micrococcus catarrhalis* in 2 cases	= 4·7	,,
The *Bacillus septus* + *Micrococcus catarrhalis* in 4 cases	= 9·7	,,
No definite organism isolated in 1 case	= 2·4	,,

Considering the acute and chronic forms separately, the following causal relationship was determined:

	Bacillus of Friedländer.	*Bacillus influenzæ.*	*Bacillus septus.*	*Micrococcus catarrhalis.*
Acute ..	Yes	Yes	Yes	Yes
Subacute ..	Yes	Rarely	Rarely	Yes
Chronic ..	Yes	No	No	No

It would thus appear that the only common cause of non-suppurative chronic nasal catarrh is the bacillus of Friedländer.

2. *Of Tracheal Catarrh.*—The *Bacillus septus* would appear never to set up this condition; the bacillus of Friedländer very exceptionally; the *Bacillus influenzæ* and the *Micrococcus catarrhalis* habitually.

It must, however, be noted that the latter of these is frequently present in perfectly heathly tracheas, just as in certain healthy individuals the pneumococcus is always to be found in their sputum. A catarrh of the trachea set up by the *Micrococcus catarrhalis* soon, moreover, becomes secondarily infected with other organisms, just as does a catarrh of the conjunctival or urethral mucous membranes. The prime factor is, however, the *Micrococcus catarrhalis*, which is also, I believe, the probable cause of many cases of bronchitis.

3. *Of the Accessory Air Sinuses.*—Lewis and Logan Turner[1] made a number of careful bacteriological examinations, both in the cadaver and on the living subject. A great variety of organisms were found, chief among which were the staphylococcus, streptococcus, pneumococcus, and bacillus of Friedländer. Just as in the case of the lachrymal duct the acute infection due to Koch-Weeks bacillus, the *Bacillus lacunatus*, *Bacillus coli*, staphylococcus, or gonococcus becomes secondarily infected by the *Streptococcus pyogenes*, which ultimately displaces the other organisms altogether, and maintains a chronic dacryocystitis, so I believe in these cases the prime infection in many cases to be due to an attack of acute nasal catarrh due to the *Bacillus influenzæ*, bacillus of Friedländer, *Bacillus septus*, or *Micrococcus catarrhalis*,

[1] *Edinburgh Medical Journal*, November, 1905.

and that the staphylococci, streptococci, and pneumococci are secondary infections, maintaining a chronic condition. This probably affords ample explanation of the fact that chronic nasal catarrhs with sinusitis fail to give entirely satisfactory results, as we shall see, with vaccine of the bacillus of Friedländer.

The Opsonic Treatment of Acute Catarrh of the Respiratory Passages.

Distressing as is the stage of acute discharge in cases of colds, the discomfort is slight compared with that of the subacute stage, when the discharge is thick and grumous and blocks up all the nasal passages. This part of an attack can, I have found, be cut down to a duration of only two or three days by the injection of a suitable vaccine. As soon as the patient is seen, smears and cultures should be made of the mucous discharge and the infecting organism ascertained. Whichever it may prove to be, the best procedure undoubtedly is to make a vaccine from the organism thus isolated. In the case of the *Bacillus septus* a stock vaccine may, however, be employed, in case of objection being taken to the expense, inasmuch as it appears to be a morphological entity. This perhaps holds, but to a less degree, in the case of the *Micrococcus catarrhalis ;* but so great are the variations exhibited by different members of the bacillus of Friedländer group that but slight success may be anticipated from any vaccine other than that prepared from the patient's own organism, unless it be one of high polyvalency. If possible, the patient should remain in bed for at least twenty-four hours subsequent to injection ; but should this not be possible, then as soon as he has arrived at home for the evening is a suitable opportunity for injection.

The negative phase with an appropriate dose being usually over within twelve or eighteen hours, risk of relapse is only slight by eight or nine o'clock the next morning. The dose I usually employ is 150,000,000 or 200,000,000 of any of the above organisms.

I have now treated a considerable number of cases in this way, and always with very marked success. Some people appear to be immune to all 'cold' organisms, others are especially susceptible to one of the group, yet others to more than one. Injection during the subacute stage of an attack in those who fall under the second of these categories has, in each instance, not only markedly cut short the attack, but entirely prevented the onset of others, even for a period of over a year. In those who are susceptible to more than one of these organisms any given attack may be due to one only of their particular enemies or to more than one. Each organism produces its own type of cold, and from the unusual features presented mixed infection can be diagnosed even before smears or cultures have been examined. Should one organism only be found in the particular attack, then a vaccine of that organism alone may be given, or to it may be added a stock vaccine of the other organism to which the patient is also susceptible. In this way the attack may be shortened, and immunity also secured against future ones. Should mixed infection be found present, then, of course, a mixed vaccine should be administered. The following are a few examples of cases treated according to this method.

Case 1 had for years been very susceptible to catarrhal attacks, which began in the naso-pharynx, producing a distinctly sore throat. A train journey, even for a few miles, would infallibly induce such an attack.

Advantage was taken of an acute attack to isolate the *Bacillus septus*, which had been diagnosed beforehand as the causal agent. Upon the third day of the attack an injection of 250,000,000 organisms was given. Two days later the patient was well. Soon after he was called upon to undertake a long and tedious train journey in the depth of winter. For the first time for years, no cold resulted, and during the subsequent nine months, despite frequent train journeys, he remained entirely immune. On one or two occasions an impending attack was felt, but immediately aborted.

Case 2 had at least half a dozen acute colds every winter, always of the same type, obviously due to the *Bacillus septus*. At the beginning of last winter an unusually severe but typical attack came on, and the *Bacillus septus* was isolated. Upon the second day of the attack his index was 0·94. Upon the fifth day he felt very bad indeed, and accordingly 275,000,000 organisms were injected. Improvement began within twenty-four hours, and was complete within forty-eight.

3 days after injection the index was 1·7
13 „ „ „ „ 1·1

Although the index would thus appear to have returned to normal within a fortnight, the immunity conferred lasted throughout the whole winter despite repeated exposure to contagion.

Case 3 had had four attacks of extreme severity within nine months. Upon one occasion the bacillus of Friedländer and *Bacillus septus* were both isolated, upon the second and third only the bacillus of Friedländer. Hardly was the patient convalescent from the third attack, which was one of the most severe colds I have ever seen, all the accessory sinuses and middle ear being involved, when

a fourth attack came on. Upon this occasion the bacillus of Friedländer and *Micrococcus catarrhalis* were present in about equal numbers. The prostration of the patient was so extreme that I decided not even to delay while a vaccine was prepared, but on the fourth day of the attack 250,000,000 each of stock vaccines of the bacillus of Friedländer and *Micrococcus catarrhalis* were administered.

For forty-eight hours the patient was very bad, but then began to improve, and mended rapidly. Four months later she informed me that on several occasions she had felt one of her old attacks coming on, but in each instance it had been aborted completely within two or three hours.

Case 4 had been a martyr to repeated attacks of 'Friedländer' colds for years. The organism was isolated during an acute attack two years ago and two injections given, with the result that only one slight attack has occurred in all the subsequent interval, and this yielded to a single injection.

Numerous other cases have been similarly treated, and all have the same tale to tell—subsequent immunity from attacks. How long such immunity lasts it is impossible to say, but it is hardly advisable to allow more than three months to pass before giving a fresh injection. A vaccine once made will keep indefinitely, so that this trouble and expense need only once be incurred in the majority of cases.

The Opsonic Treatment of Tracheal Catarrh.

Tracheal catarrh, as we have seen, is usually initiated by the *Micrococcus catarrhalis;* unfortunately, however, secondary infection by other organisms often adds a complicating factor. The treatment is rather difficult and results not very encouraging; the best that can be hoped

for is diminished secretion and comparative freedom from acute attacks of tracheitis.

Treatment may be carried out either by means of a vaccine prepared only from the *Micrococcus catarrhalis* isolated from a suitable specimen of tracheal mucus, or by a combined vaccine of the various organisms present. In the former case injection is begun with 150,000,000 to 250,000,000 organisms, and is, of course, controlled by determinations of the index to the *Micrococcus catarrhalis*. In the latter case a minimal dose of 250,000,000 of the mixed organisms is used at first. Inasmuch as the estimation of the indices to the various organisms would be far too tedious, that to one alone may be selected—best to the *Micrococcus catarrhalis*. A tri-weekly interval between injections will, however, prove sufficiently accurate. By means of such a combined vaccine I have secured a certain measure of success in two cases of chronic tracheitis, diminishing the discharge, and preventing the occurrence of any acute exacerbations. In a third case cure was complete. That extremely troublesome complaint of children whooping-cough would appear to offer exceptional opportunities for opsonic treatment. So far as I am aware no experiments have, however, been made in this direction.

The Treatment of Chronic Nasal Catarrh.

This, as has been mentioned, is apparently always due to the bacillus of Friedländer. In cases where the accessory air sinuses are not involved, complete cure, both of the chronic attack and of the acute exacerbations, is to be expected from opsonic treatment and daily douching with weak antiseptic washes, such as glycothymoline. By these means I have completely cured cases of even

ten years' standing. The index in such cases is usually above normal and between 1·2 and 1·4. A dose of 250,000,000 of the patient's own organism will usually raise this to 2·5 or over, and produce marked improvement within a week. Two or three such injections should prove sufficient.

When, however, extension has taken place to the frontal, ethmoidal, or antral sinus, the case is very much more difficult. In two such cases of about twenty years' standing I have sterilized the nose by adequately raising the index, only, however, to find it reinfected in a month or two from the accessory sinuses. Could free drainage from these be secured, complete cure might be expected; as it is, the poor blood-supply and lymph-flow to the parts do not bring sufficient opsonin to insure the death of the infecting organisms. Perhaps very prolonged treatment might secure this much-desired result. One very important result is, however, certainly secured, and that is the prevention of acute outbursts of the nasal catarrh.

It remains to mention that the list of organisms given above as being capable of the production of acute nasal and tracheal catarrh is not quite complete. It comprises all the organisms met with by the author during four years extensive experience of London epidemics. Benham [1] has recorded an epidemic occurring in Brighton, which appeared to be due chiefly to the *Micrococcus paratetragenus*,[2] which he succeeded in isolating from a number of his cases. He informs me that the symptoms due to this organism closely resemble those I have described as characteristic of the *Micrococcus catarrhalis*.

[1] Proc. Brighton and Sussex Med.-Chir. Soc., 1907-08, p. 84.

[2] Besançon and De Jong: *Bull. Soc. Méd. Hôp. de Paris*, March 2 and 16, 1905.

CHAPTER XII

THE COLON, TYPHOID, AND DYSENTERY GROUPS

THE investigations of Gaertner, Achard and Bensusan (1896), Gwyn (1898), Schottmuller (1900), Kurth (1901), Bryon and Kayser (1902), and others have revealed the existence of several organisms which occupy an intermediate position between the *Bacillus coli communis* on the one hand and the *Bacillus typhosus* on the other. Some of these in their characteristics more nearly resemble the colon bacillus, and are therefore known as paracolon bacilli; others more nearly resemble the *Bacillus typhosus*, and are known as paratyphoid bacilli (*A* of Bryon and Kayser, *B* of Schottmuller). In addition to these are the various members of the dysentery group (Shiga, Flexner, Hiss, Kruse).

The fact that these intermediates are capable of causing lesions in the human subject, as yet imperfectly defined, causes them to assume an added importance. The differentiation of the various members of this group the one from the other, is by no means easy, and hardly comes within the scope of this small book. For convenience the Colon, Typhoid, and Dysentery groups will be described as if sharply defined from each other.

I. THE BACILLUS COLI COMMUNIS GROUP.

The *Bacillus coli communis* and its near allies are especially associated with disease of the abdominal

organs, setting up such conditions as peritonitis, cystitis, urethritis, endometritis, abscesses in and around the kidneys, enteritis, perityphlitis, and inflammation of the gall-bladder and its ducts. It also occasionally is the cause of empyema, puerperal fever, and even suppurative periostitis.

The first cases of the successful application of vaccine therapy to coli infections were those recorded by Wright[1] as under :

1. One of cholecystitis, which had continued for sixteen years.

2. One of acute coli infection of the biliary passages, where, after removal by operation of an impacted calculus, the fever and jaundice continued, and the bile was flowing away through the external wound, probably from plugging of the bile-duct by inspissated mucus.

3. One which had been operated upon two months previously, fourteen stones being removed from the gall-bladder. The sinus remained open, and the patient made little improvement. An injection of 200,000,000 organisms was given, and the index raised to 1·8. Closure of the sinus was followed by a rise of temperature and reopening of the sinus. A second injection produced reclosure of the sinus. A rigor then occurred, and the sinus again opened. Owing to self-inoculation the index rose to 4, subsequently falling with final closure of the sinus.

Among the cases subsequently recorded the following may be mentioned :

Western (*loc. cit.*) mentions two cases. The first had had cystitis for fifteen months, and had been treated with urinary antiseptics without any benefit. Three months' vaccine treatment caused complete disappearance of the

[1] Pathological Society, January 16, 1906.

Bacillus coli communis from the urine, and there has been no recurrence.

The second had had cystitis for ten months. Vaccine treatment was incomplete, but had produced very marked improvement.

Turton (*loc. cit.*) records four cases :

No. 1 had been operated on for gall-stones, but the pain, sickness, and rigors persisted, in so much that the patient was not expected to live. Three injections of *Bacillus coli communis* vaccine were given. After the first the rigors ceased, and in four weeks the patient was perfectly well.

Nos. 2 and 3 were cases of appendicular abscess. In one the condition was desperate, but both did well.

No. 4 was a case of cystitis of six months' duration, which, after eight injections, cleared up completely.

Butler Harris[1] draws attention to the interesting fact that in many cases of slight endometritis with cervical catarrh the colon bacillus is present, and fall in the index to this organism is coincident with depression of the local and general condition. He finds that 5,000,000 of a vaccine given a week after the period and repeated a week before will cure the local infection and improve the general health. The treatment has, however, to be continued for a considerable time, perhaps six months. He also states that in mucous colitis good results have been obtained.

Bonney[2] draws attention to the grave import of the *Bacillus coli communis*, complicating a primary infection by streptococci or pneumococci in puerperal fever. The colon bacillus alone may, however, be responsible for this condition.

[1] *Practitioner*, May, 1908, p. 647.

[2] *Clinical Journal*, August 19, 1908.

The scope for vaccine therapy in this severe infection would appear to be great, but accurate diagnosis of the infecting organisms in a prime necessity.

Wright and his co-workers have recently been applying index determinations as a diagnostic aid in cases of supposed appendicitis and appendicular abscess.

The advisability of raising the opsonic index to the colon bacillus, prior to abdominal operations in cases where contamination of the wound is feared, is worthy of earnest consideration. A dose of 50,000,000 to 100,000,000 of vaccine three to seven days previously will suffice.

The following case of infection by the *Bacillus coli communis* is not without interest: The patient was sent to me by Mr. Wyndham Powell, suffering from subacute urethritis, for treatment with a gonococcal vaccine. Four injections were given, the index being raised from 0·37 to 1·6. The urethral condition was decidedly improved, and the discharge practically ceased. Considerable discomfort, however, was felt in the region of the prostate, and finally culminated in an attack of acute prostatitis and cystitis. Nothing definite could be felt per rectum. The colon bacillus was isolated from the urine, and 200,000,000 of an autogenous vaccine given. A rigor and severe general disturbance resulted. This would appear to be especially liable to happen in this infection and to denote closure of a sinus or suppressed discharge, and re-examination per rectum revealed a small nodule in the prostate. Upon this breaking down and discharging, improvement began, and two injections, one of 100,000,000, the other, fourteen days later, of 150,000,000, resulted in cure.

Cases of bacilluria are commonly due to *Bacillus coli*

communis, especially when cystitis complicates tuberculosis of the bladder or kidney. In these instances little progress is often made under tuberculin treatment alone. Upon attention being simultaneously directed to the colon infection, marked improvement soon results.

Owing to the apparent liability to rigors and great constitutional disturbance of these cases when an injection results in suppressed discharge, an initial dose of 50,000,000 should not be exceeded; subsequently larger doses at ten days' interval are to be recommended. The best results will only be obtained by the use of an autogenous vaccine.

II. Infections by the Typhoid Group of Bacilli.

The most important members of this group are the *Bacillus typhosus abdominalis* (Eberth), the *Bacillus paratyphosus A* (Bryon and Kayser), and *Paratyphosus B* (Schottmuller). Other slightly variant forms have also been described. The practical importance of the discovery of these different members is very great, and especially with regard to the question of the production of anti-typhoid immunity. Epidemics of pseudo-typhoid fever have been described from Germany,[1] France, and America, and isolated cases have been reported in Great Britain, India, etc. The paratyphoid fevers have occurred in series of true enteric fever, in house epidemics, and under circumstances which point to the disease being sometimes water-borne.

The clinical features have been very variable, but three types may be described:

Type I. closely resembles mild typhoid fever, and can

[1] Hunerman, *Zeitschrift f. Hyg. u. Infect. Krankh.*, 1902, Bd. xl., p. 522; and Schottmuller.

only be distinguished by failure of the blood-serum to agglutinate the *Bacillus typhosus*, and its power to agglutinate one of the other organisms of the group. As these cases all recover, the anatomical lesions are unknown. Hæmorrhage, phlebitis, and relapse have been described as complications.

Type II. presents the clinical features of septic infection, and resembles the so-called typhoid septicæmia, or enteric fever with intercurrent or terminal sepsis. These sometimes end fatally. Enlargement of the spleen is a constant feature; sometimes the intestines are normal, at other times ulcerated, but the ulcers are like those due to dysentery rather than to typhoid, the solitary follicles, Peyer's patches, and mesenteric glands being as a rule unaffected.

In both Types I. and II. rose spots and sore throat are very prominent features.

Type III.—In these cases the organisms have been found in abscesses in patients in whom no history of enteric fever was obtainable.

Both in true enteric and in the fevers of Types I. and II. the organisms can be almost invariably isolated from the blood according to the following method: The medium employed is ox bile, 90 c.c.; glycerine, 10 c.c.; peptone, 2 c.c. Twenty c.c. of this are put into small flasks and sterilized. About 9 c.c. of blood is then withdrawn from a vein in the antecubital fossa, with aseptic precautions, and 3 c.c. run into each of three flasks, which are then incubated for twelve to twenty-four hours. Stroke cultures are then made on a litmus lactose agar plate, upon which growth may often be seen in six hours.

Coleman and Buxton[1] employed this method in a large

[1] *American Journal of Medical Science*, June, 1907.

series of cases, and isolated the organism in every instance before the second week of illness, and often before the serum reaction developed. After the second week there are much fever organisms in the blood. Ninety per cent. of thirty-three relapses also gave a positive result.

Failing to isolate the organisms by blood-culture, it remains to attempt their isolation from the urine and fæces according to the approved methods.

Having obtained a culture, test is then made for the Widal reaction, both with the organism and with a standard strain of the *Bacillus typhosus*. For it must not be forgotten that the patient may be infected with both the *Bacillus typhosus* and *Paratyphosus*.[1]

In Europe the *Paratyphosus B* appears to be the commoner. In India, Semple[2] found the *Paratyphosus A* in four cases, the *Paratyphosus B* in two cases.

Antityphoid Immunization.

Of the bearing of these results upon the statistical side of therapeutical immunization against enteric fever sight must not be lost. As to the merits or demerits of the procedure, considerable diversity of opinion has existed. The latest statistics, and especially those recorded by Luxmore[3] in the case of the 17th Lancers, are much more favourable; but before any definite conclusions can be formed it is obviously necessary to take into account the possibility of a given epidemic, or of a certain number of cases in such an epidemic being really due to one or other of

[1] For such a case see *Scientific Memoirs of the Medical Department of Government of India*, No. 32, 1908, p. 31.

[2] *Ibid.*

[3] *Journal of Royal Army Medical Corps*, January to June, 1907, p. 492.

the paratyphoid bacilli, and to this hitherto no attention has been paid. The advisability of employing a vaccine containing not only the *Bacillus typhosus*, but also the several paratyphoid bacteria, is worthy of consideration.[1]

Preparation of Antityphoid Vaccine: its Effects and Method of Use.

The mode of preparation approved by the Army Council is as follows: A non-virulent strain is grown on broth of a definite reaction, and incubated at 37° C. for twenty-four to forty-eight hours. In order to encourage free growth special flasks are used, giving a shallow layer of about 1 inch of medium, so as to permit of good aeration, this being essential to obtain maximum development. The contents of the flask are then standardized in the usual way, and sterilized by heating on a water-bath for one hour at 53° C. Sterility is proved by aerobic and anaerobic cultures, and 0·25 per cent. lysol added. The vaccine is diluted if necessary so as to contain 1,000,000,000 bacteria per c.c., and put up in glass bulbs containing 1 c.c. and ½ c.c. respectively.

To insure antityphoid immunity the smaller dose is injected into the flank or side of the arm, and the patient put to bed for twenty-four hours, as sometimes considerable constitutional disturbance results. Ten days later the larger dose is given, and should produce no ill effects.

The *effects of such inoculation* have now been fully studied. The method of estimating the typho-opsonic index is a special one, and will be found in the Appendix. The phagocytic index[2] appears to be depressed for

[1] A vaccine of this composition can now be obtained from W. H. Martindale, 10, New Cavendish Street.

[2] Harrison, *Journal of Royal Army Medical Corps*, May, 1907, p. 472.

three to six weeks after commencing treatment, and then rises above normal. There is also a marked rise of four to six times in the bactericidal power.

The duration of the immunity thus conferred has been studied by Harrison.[1] He found that evidence of a bactericidal activity higher than normal and of agglutinins could be obtained from the serum of men who had been inoculated as long as six years previously; but whether the protection that so remains will still suffice to ward off an attack of enteric fever is not yet known.

The rôle of agglutinins and bactericidal substances in the production of typhoid immunity is still unsettled. Thus, Jorgensen[2] found that the agglutinating power usually declines after the third week, and that a high agglutinative power does not appear to protect against relapse or recurrence, and the same is possibly true of the bactericidal substances; while Stern and Korte[3] found in a patient, whose serum revealed the highest bactericidal power ever observed by them, that a relapse developed eight days later. A possible fallacy in these observations lies in the fact that they were conducted '*in vitro*.' Topfer and Jaffe[4] found with the Pfeiffer method '*in vivo*' that the serum of convalescents was more effective bactericidally than that of acutely ill typhoid patients; while Klein,[5] and Neufeld and Kuhne,[6] have found increase of opsonin, and especially of specific opsonin, in the 'immune' sera of convalescent cases.

[1] *Journal of Royal Army Medical Corps*, May, 1907, p. 472.
[2] *Centralb. f. Bakt. u. Parasit.*, Jena, 1908, Bd. xxxviii., p. 475.
[3] *Berlin. Klin. Woch.*, 1904, Bd. xli.
[4] *Zeitschrift f. Hyg. u. Infect.*, Leipzig, 1906, Bd. lii., p. 393.
[5] *Johns Hopkins Hospital Bulletin*, June and July, 1907, p. 245.
[6] *Arb. a. d. k. Gesundheitsamte*, Berlin, Bd. xxv., p. 164.

Typhoid Carriers.

A careful study of recent epidemics has revealed the fact that in many cases these have been initiated by the contamination of food or water supplies from the urine or fæces of old enteric patients, who in some instances have exhibited no symptoms for many years. Semple has carefully investigated several of these cases, and finds that this discharge of bacteria may be very markedly intermittent, occurring at intervals perhaps of a month apart. He explains this as follows: The typhoid bacilli during an attack are deposited in the liver or kidney; in the former case they may infect the bile, a most favourable medium for their growth, and are poured into the intestine and excreted in the fæces. In the latter case an infected focus breaks down at intervals and infects the urine. In confirmation of this view is the fact that he examined the bile in seventeen fatal cases of enteric, and found it infected in ten of these.

As a result of these investigations, the question of careful systematic testing of the urine and fæces of convalescent typhoid cases, and of the therapeutic inoculation of all such as are found to continue to be infected, becomes a very important one.

The treatment of enteric fever with specific sera, filtrates, and residues has been studied in a series of 204 patients by Richardson.[1]

Of these 204 cases, 74 underwent ordinary routine treatment; 35 routine treatment, together with the sera of immunized horses given in various ways; 74 routine treatment, combined with subcutaneous injections of about 3 c.c. daily of a sterile filtrate of bouillon cultures;

[1] *Boston Medical and Surgical Journal*, vol. cvii., No. 14, p. 449.

21 routine treatment, combined with daily subcutaneous doses of 2 to 10 c.c. of typhoid vaccine.

The administration of these immunizing agents was uncontrolled by index determinations.

His conclusions are most guarded, but are as follows: That, despite the handicap to specific therapy in the difficulty of early diagnosis—

1. Specific therapy, confined to the original disease, increases, apparently, the tendency to relapse.

2. Inoculation with typhoid vaccine continued into convalescence largely eliminates the risk of relapse.

3. Antityphoid serum is no more effective than filtrates or vaccine, and is much more expensive.

4. Typhoid filtrates may exert a powerful effect upon the clinical course, their use being followed in many instances by chills or rise in pulse and temperature, these being often followed in their turn by marked fall in pulse-rate and temperature, and a general improvement in the clinical picture.

5. That a vaccine seems to make the typhoid process longer, but milder, and is apparently very effective in the prevention of relapses.

Vaccine therapy also finds a place in the treatment of cholecystitis, which is much more frequently due to the *Bacillus typhosus* than is commonly supposed.

In localized infections the same dosage as for *Bacillus coli communis* may be employed.

III. The Dysentery Group.

Of the various forms of dysentery, the only one with which vaccine therapy is concerned is the bacillary. Several closely-allied bacteria, differing mainly in their

sugar and agglutinative reactions, have been described in different epidemics by Shiga, Kruse, Flexner, Hiss, and Strong, and bear their respective names.

The chief work from the point of view of immunization by means of vaccines has been done by Captain W. H. C. Forster, of the Indian Medical Service. During the past two years he has been actively engaged upon the subject, and to his publications and letters I am indebted for the following account :

Clinically, bacillary dysentery may be divided as follows :

Class. I. Acute dysentery—

1. Gangrenous.
2. Non-gangrenous.

Class. II. Chronic dysentery, which may be subdivided into—

1. Cases of weeks' or months' duration, in which the patient is still passing dysenteric stools, either continuously or intermittently.
2. Cases of years' duration, in which the patient has ceased to pass dysenteric motions, and in whom the symptoms consist of flatulent diarrhœa, accompanied by abdominal pain of a peculiar type.

Of these, the following are suitable for vaccine therapy :

The non-gangrenous cases of Class I. which have resisted treatment for seven days, and in which the patient is not obviously moribund.

Of Class II. all cases are suitable except those in whom the bowel is so extensively damaged by chronic ulceration as to render hopeless treatment of any sort.

Although the cases treated have been variously in-

fected by the following different strains—Kruse-Shiga, Flexner, and Y. of Hiss—the vaccine employed has been prepared only from the Kruse-Shiga type ; so that the results achieved are the more striking. Uniformly satisfactory results have been obtained and recorded by Forster,[1] Gillitt,[2] Stephen,[3] Newman,[4] Castellani,[5] many of the cases being very striking, especially in the chronic relapsing ones, in which all medical treatment had been unavailing. Thus, of ten such chronic cases Forster completely cured seven, these remaining perfectly well for twelve months after treatment.

In the Midnapore Gaol the case mortality over six years averaged 6·3 per cent. ; after the adoption of Forster's vaccine it fell to 0·9 per cent.

The scheme of treatment laid down by Forster is as follows : The immediate injection of acute as well as of chronic cases by means of a stock vaccine, given in small doses at fixed intervals, without the control of the opsonic index. Of course common sense must be applied if clinical symptoms contra-indicate the repetition of a dose at a given time. In acute cases the commencement of vaccine therapy is contra-indicated from the fourth to the twenty-first day.

As different strains of the organisms vary greatly in their toxicity, and as toxic strains are liable to produce very violent local and general reaction, even in small doses, counting methods of standardization are not employed, but the strength of the vaccine is so regulated that the minimum lethal dose for a rabbit of 1,200 to 1,400

[1] *Indian Medical Gazette*, June, 1907, p. 201.
[2] *Ibid.*, January, 1908, p. 12. [3] *Ibid.*, October, 1907, p. 375.
[4] *Lancet*, May 16, 1908, p. 1410.
[5] *Archiv f. Schiff u. Trop. Hyg.*, Bd. xi., Heft 3.

grammes in weight is not less than 0·4 c.c. Of such a vaccine his dosages are, for an adult, in both the acute and chronic forms—

First dose	0·1 c.c.
Second dose	0·2 c.c.
Third dose	0·3 c.c.
Fourth dose	0·4 c.c.

For females a slight reduction is necessary.

In the case of a child of nine, a first dose of 0·05 c.c. was given, and a second of 0·1 c.c., without ill effects and with a good result.

The doses indicated above produce practically no negative phase, and in fourteen days the immunity is more than a hundred times what it was before the dose.

Forster employs intervals of ten days between the doses, and usually proceeds to the fourth dose, to make sure that the patient has got rid of all bacilli and is not likely to become a chronic 'carrier.' If it be necessary to go beyond the fourth dose with increased quantities, the bowel symptoms must be carefully watched, as large doses are very toxic, and in animals, at all events, badly tolerated. In man, the symptoms of over-dosage take the form of dysenteric pains in the bowel, with diarrhœa and even blood and mucus. Most doses are followed by some slight symptoms of the sort, but if these are severe in any given case, a reduced dosage must be employed.

CHAPTER XIII

INFECTIONS DUE TO THE *MICROCOCCUS MELITENSIS*, *BACILLUS PARALYTICANS*, *MICROCOCCUS NEOFORMANS*, *MENINGOCOCCUS*, AND *ACTINOMYCOSIS*

THE MICROCOCCUS MELITENSIS.

THE fact that Malta fever is a systemic infection would seem to render vaccine therapy inadvisable. Wright, however, advocates its use in comparatively light attacks, when the fever is likely to run on for months without any severe intoxication of the system, and where the imperfect development of the agglutination reaction seems to indicate that the immunizing impulses are in default.

He has successfully treated a case of localized infection supervening upon an attack of Malta fever.

Bassett Smith,[1] following up the apparently successful treatment by Reid of nine cases of Malta fever by means of a vaccine, observed the results of such treatment in sixty-one cases, to which 224 injections were given. These cases comprised all grades in the disease, from the severe undulant type to the intermittent. The initial dose employed was usually about 50,000,000 organisms, and this was but rarely exceeded, the interval between the injections being ten days. The negative phase was

[1] *Journal of Hygiene*, January, 1907, p. 115.

frequently very short or altogether absent, a steady rise being commonly observed.

No relationship was found to exist between the curves of the opsonic indices and the agglutination reactions of the patient's sera. Bassett Smith concluded that the vaccine treatment of Malta fever appears in a certain number of cases to produce a beneficial result, the severity of the symptoms being diminished, the general condition improved, and the duration of the disease curtailed; but that in the more severe type of case, with high fever and evidence of severe intoxication, the method appears to have a deleterious instead of a favourable action.

I would suggest that the more frequent administration of much smaller doses, as in streptococcal and gonococcal septicæmias, might possibly secure more favourable results.

The Bacillus Paralyticans.

Numerous attempts have been made to isolate from the blood and cerebro-spinal fluid of cases of general paralysis of the insane and of tabes dorsalis an organism or organisms which might prove to stand in a causal relationship to this disease or to the congestive seizures.

Ford Robertson and McRae claimed to have demonstrated the constant presence of an organism of the diphtheroid group, to which they gave the name *Bacillus paralyticans*, in the blood, cerebro-spinal fluid, and brain tissues. Other observers, among whom may be mentioned Eyre and Flashman, have, however, shown that there is hardly any part of the body where diphtheroid organisms had been obtained by Robertson in cases of general paralysis from which similar organisms could not

be obtained in cases free from any semblance of insanity. The difficulties in technique are so great, and the risks of contamination in taking cultivations so considerable, that variable results are almost inevitable in the hands of different observers. It may be mentioned that the psychological moment for taking cultures is as soon as possible after a congestive attack, for leucocytosis is rapidly developed, and in an hour or two the phagocytic action of the leucocytes may destroy all the organisms in the blood-stream. Sufficient attention to this point does not appear to have been paid by all observers. Ford Robertson now considers that a second organism, to which he has given the name *Bacillus paralyticans brevis*, is also concerned in the production of a certain proportion of cases of general paralysis. Candler[1] altogether failed on forty-one occasions in twenty-four cases to find either of these organisms, while G. M. Robertson[2] upon fifteen occasions in seven cases of undoubted general paralysis recovered a diphtheroid organism from the blood or cerebro-spinal fluid, which, however, appeared to differ from either of Ford Robertson's forms. Sufficient evidence has not yet been accumulated to warrant the view that any definite member of the diphtheroid group is responsible for the production of general paralysis, although it seems likely that the presence of these organisms is more than a coincidence, and important discoveries may soon be anticipated.

O'Brien[3] details the result of opsonic determinations with Ford Robertson's original *Bacillus paralyticans* upon seven cases of this disease. The indices showed great fluctuations, leading him to the conclusion that the infec-

[1] *Lancet*, August 17, 1907, p. 450. [2] *Ibid.*, p. 449.
[3] *Journal of the American Medical Association*, 1906, p. 2180.

tion is a systematic one. Injections of a vaccine were given about every fourteen days, and marked improvement in the symptoms claimed to be noticed.

These results must be received with great caution, in view of Ford Robertson's modified opinion of the causal relationship of this organism to the disease, and in consideration of the fact that remissions in the course of general paralysis are very common. In so dread a disease no chance of doing good should, however, be neglected, and in the event of the isolation of a diphtheroid organism from cultures of the cerebro-spinal fluid taken during or immediately after a congestive attack, the administration of a vaccine prepared from this organism would appear to be a justifiable—nay, advisable—proceeding.

The Micrococcus Neoformans.

The contention of Doyen that this organism is the true cause of carcinomatous tumours has not been accepted by pathologists in this country; for not only is it found in the vicinity of carcinomata, but also in that of sarcomata and such benign growths as adenomata. Inoculation experiments upon rats and mice have also completely failed to produce a malignant tumour.

Successful treatment by means of a vaccine was recorded by Wright in a case of cancer of the larynx. Death, however, ensued in about six months, and was found post-mortem to be due to cancer.

Jacobs and Geets [1] recorded the results of treatment in thirty-seven cases of mammary carcinoma. They regard the *Micrococcus neoformans* as the cause of the cancerous cachexia. The index in these cases was found usually

[1] *Lancet*, April 7, 1906, p. 964.

to be below 0·8. Cases in which the index failed to rise after two injections they considered hopeless from exhaustion of the defensive powers.

The results of treatment seem to be decrease of surrounding infiltration, reduction in the size of the nodules, which usually become freely movable, great improvement in the patient's appearance and general condition, and diminution of pain. This they hold to be the time for operation. They tabulate their results as follows :

'Cure' maintained after several months in	7	cases.
Lasting improvement in	12	,,
Transient result in	7	,,
No result in	11	,,
Total	37	,,

The opinion at the London Cancer Hospital is that as a curative agent a vaccine of the *Micrococcus neoformans* is valueless, and its employment has therefore been entirely abandoned at that institution. It may, however, well be left to any inoperable case of cancer to decide whether employment of this harmless agent shall be made, in the remote hope of the case being brought within the zone of operability. Admitting that the *Micrococcus neoformans* is not the cause of cancer, it cannot, however, be denied that it is almost always associated with the cancerous tumour.

The Meningococcus.

The complete failure of various varieties of anti-meningococcic sera to influence favourably the course of the disease during the recent epidemics at Belfast and Glasgow, and the occasional success of a streptococcal vaccine in cases of streptococcal septicæmia, have encouraged efforts in a similar direction in cases of cerebro-

spinal meningitis. Rundle and Mottram[1] have recorded a successful result in a case in which the prognosis was distinctly bad. The index was 0·7 when an injection of 200,000 organisms was given; next day it had risen to 1·5. In the subsequent twenty days four doses of 500,000 organisms were given, each followed by negative and positive phases. Recorded cases of successful treatment are so far very few, but I have heard privately of two other such instances.

Houston and Rankin,[2] Fordyce,[3] and others have studied the opsonic and agglutinative power of the blood-serum and cerebro-spinal fluid in cases from various epidemics. With normal serum phagocytosis is extremely slight, and does not occur until degeneration of the coccus has commenced. This is true, irrespective of whether the organism has been freshly isolated or repeatedly subcultured. With 'immune' sera the degree of phagocytosis very rapidly increases with the extent to which the organism has been subcultured. The difficulty of some observers with clumping of the emulsion is very greatly obviated by employing a growth six to ten hours old and incubating the opsonic mixture for only ten minutes. Employing this technique, the author has not experienced the slightest trouble, even with the most freshly-isolated organisms.

At the very onset the index is probably low. Thus, in one instance Fordyce found an index of only 0·4 within twenty-four hours of onset. Later the index of the blood-serum rises very rapidly and within five or six days may be between 5 and 10. Later it may be as

[1] *Lancet*, July 27, 1907, p. 220.

[2] *British Medical Journal*, November 16, 1907.

[3] 'International Clinics' (eighteenth series), vol. i., p. 40.

high as 30 or 40. The agglutinative power of the serum is also very marked. In convalescent cases these typical reactions disappear rapidly. The cerebro-spinal fluid has very much lower opsonic and agglutinative power than the blood-serum, and may even have none at all; Houston and Rankin conclude that these reactions are of very great value in the diagnosis of early cases of true epidemic cerebro-spinal meningitis, and in differentiating them from those of posterior basic meningitis, which are due to a Gram-negative coccus very closely resembling the true meningococcus, both morphologically and culturally.

Owing to the rapid loss of virulence on the part of this organism, the vaccine should be prepared from a first subculture, if possible, and preferably from the patient's own organism.

The appropriate dosage is as yet uncertain. It is perhaps advisable to begin with 500,000 to 1,000,000, and repeat and increase as the index or clinical symptoms indicate.

The benefit observed in certain instances from lumbar puncture may perhaps be due to replacement of cerebro-spinal fluid of low opsonic power by fresh fluid with more active bactericidal properties.

Actinomycosis.

The first case of actinomycotic, or rather streptotrichotic, disease treated by means of a vaccine has been that of the lung, and probably of the liver, described by Wynn.[1] The infection probably dated back at least twelve months, and six months prior to admission to hos-

[1] *British Medical Journal*, March 7, 1908.

pital extension seems to have occurred from the bronchi to the lung tissue, and much sputum with a feculent odour was expectorated. Subsequent formation of an empyema required operation, and from the pus a pure culture of streptothrix was isolated, and a vaccine prepared from a forty-eight hours' old agar culture. The dose employed for each inoculation represented 0·001 milligramme of bacterial substance. Attempts were made to estimate the index, which was approximately 0·3 on January 3 and 0·5 on January 7; on January 8 the first inoculation of 0·001 milligramme was given. Twenty-four hours later the negative phase was apparently over, as the index had risen to 0·7, and by January 16 was 1·2. In a few days the cough became less troublesome, and the sputum and discharge of pus diminished in a remarkable way. The temperature dropped from over 100° F. to normal, and remained normal for three days. Four days after injection the discharge had so diminished that the drainage-tube was removed. A slight rise of temperature resulted, and on the 18th instant a second inoculation of 0·001 milligramme was given. Three days later temperature was again normal, and remained so. Subsequent injections were given on February 11 and 25, and March 11 and 27, each of 0·001 milligramme. The patient gained 1 stone 6 pounds in weight, and the condition on discharge was a thickened pleura, with a large, dry cavity in the lung. There was no sputum, and only occasionally a dry cough. The patient has continued well.

Short[1] points out that streptothricial infection of the human subject is much commoner than usually supposed, and that probably over 2 per cent. of all cases of perityphlitis are due to it. The disease, though very

[1] *Lancet*, September 14, 1907, p. 760.

chronic, ends fatally in quite 60 per cent. of the cases within nine months. He also describes a case of actinomycosis of the lungs in which the signs were those of broncho-pneumonia, except that the dulness was uniform. The temperature was high, and the result fatal within a few weeks.

In view of Wynn's success with vaccine therapy, the importance of making careful search for granules and mycelia in obscure lung and appendicular cases is obvious.

CHAPTER XIV

VACCINE THERAPY IN EYE DISEASES

OPHTHALMIC surgeons would probably be the first to admit that little further progress in ophthalmology is to be expected from surgery pure and simple. The prime essential is increase of knowledge in the pathology of such conditions as trachoma, Mooren's ulcer, spring catarrh, and sympathetic ophthalmia. Should a bacterial origin be established for these, treatment upon opsonic lines will hold out considerable promise of success.

The scope for vaccine therapy in diseases of the eye is already great, and is steadily increasing. The first essential for its success is accuracy in the determination of the infecting organism or organisms. In cases of doubtful tuberculosis the opsonic index does not always help ; how variable it may be is shown in Table XVI. (see page 216).

The explanation of this is that the tendency in bacterial diseases of the eye is for the index to be raised. In tuberculosis, however, the ocular infection is often complicated by chronic infection elsewhere, either of the glands, lungs, or bones, which tends to the production of a lowered index. These two factors, working in opposite directions, may result in an index within the normal limits.

The discovery of Calmette's ophthalmo-reaction (p. 102) promised to be of great service. Thus Brunetière[1] has

[1] *Gaz. Hebd. de la Soc. Méd. de Bordeaux*, July 18, 1907.

recorded its value in discriminating between interstitial keratitis due to syphilis and to the tubercle bacillus. Anbault and Lafon[1] obtained positive reactions in a case of solitary tubercle of the choroid, in two of phlyctenulæ, in episcleritis, in tubercular interstitial keratitis, and in optic neuritis with a choroidal nodule ; also in four cases of healed phlyctenule. Stephenson[2] has employed it in over thirty cases, among which were six cases in children of relapsing ulceration of the cornea. A positive result

TABLE XVI.

Case.	Nature of Case.	Index.
1	Interstitial keratitis	2·2
2	Phlyctenules	1·9
3	Kerato-iritis with mutton-fat deposits	1·4
4	Choroidal nodule	1·25
5	Kerato-iritis with phlyctenules	1·1
6	Tubercular cyst of iris	0·87
7	Neuro-choroidal retinitis	0·8
8	Choroidal tubercle	0·7
9	Interstitial keratitis	0·7
10	Keratitis with glands in the neck	0·55
11	Keratitis with cervical and abdominal glands	0·5

was obtained in each case, though only two of them showed tubercular lesions elsewhere. In one case of recent phlyctenular keratitis the result was negative. In three cases of choroiditis in young women, free, apparently, from traces of syphilis, the reaction was positive, though no tuberculous focus could be found elsewhere. Of eight cases of interstitial keratitis, five showed obvious signs of inherited syphilis, and in these the result was negative ; in the three others it was positive.

[1] *Gaz. Hebd. de la Soc. Méd. de Bordeaux*, July 18, 1907.

[2] *British Medical Journal*, October 19, 1907, p. 1038

Of three cases of episcleritis one had enlarged cervical, axillary, and inguinal glands, and the result was positive; in the two others it was negative.

One case of tubercle of the iris, one of tubercle of the cornea, and two of chronic irido-cyclitis also gave positive results.

Two important considerations, however, militate against its use in ophthalmic surgery. The first is that it is a test for the presence of an active tuberculous focus anywhere in the body, and, inasmuch as syphilitic keratitis and tuberculous adenitis may well be coexistent, positive result cannot be taken as indicating certain ocular tuberculosis. The second objection is that the test is now regarded as inapplicable to any but a perfectly healthy eye, and the advisability of applying it to the other eye when one is diseased is still a matter of doubt. Should this be decided upon, it is advisable to use a more dilute tuberculin than is ordinarily employed. A first application may be made of a solution of 1 in 500. Should no reaction occur, a second may be made of double this strength; beyond this it is hardly advisable to go, as several cases of severe corneal ulceration or irido-cyclitis have now been reported from the use of a 1 per cent. solution.

A positive reaction is to be considered merely as indicating an active tuberculous focus somewhere in the body. A negative reaction with a solution of 1 in 250 is not to be held as proving the absence of tuberculous infection, but only as confirmatory evidence of its absence.

Assuming the diagnosis of tuberculosis to be established, several questions of importance require consideration, viz.:

1. Is the control of index essential ?
2. The variety of tuberculin to employ.
3. Dosage and interval in default of index determination.

As regard the first of these, I am personally always loath to undertake cases of this nature without the control of the index, for two reasons : Firstly, the dosage is by no means easy to regulate from clinical symptoms ; and, secondly, the negative phase is often of unusual length, even with minimal doses.

As regards the second point, we are quite ignorant of the variety of the tubercle bacillus at work in ocular tuberculosis. Probably it is sometimes the one variety, at another time the other variety. This consideration induced me to give trial to the mixed T.R.'s in equal proportions ; the results in the few cases in which it has so far been tried have been so uniformly better than those previously obtained that I now make exclusive use of this preparation. Nor is this all ; certain cases there are, such as solitary tubercle of the choroid or iris, where toxæmia is altogether absent, and the efforts need only be directed towards the destruction of the bacilli at the infected focus ; but other cases there are, such as severe episcleritis, especially when these are secondary to tuberculosis elsewhere, in which toxæmia appears to play an important part. In these, therefore, I now combine Denys' tuberculin in conjunction with the mixed human and bovine T.R.'s, as this preparation possesses powerful antitoxin-exciting properties.

As regards the third of the above questions, while the best results certainly cannot be obtained without 'indical' control, yet the following scheme of treatment will, as a rule, secure a good result :

If toxæmic symptoms be absent, begin with a dose of 0·00001 c.c. of mixed human and bovine T.R.'s; repeat in twenty-one days; double the dose after another twenty-one days; and, if all goes well, repeat this doubled dose in seventeen days. Then proceed cautiously, guided by symptoms, increasing the dosage and diminishing the intervals only very gradually.

In cases such as severe episcleritis or irido-cyclitis, combine with the T.R.'s a small quantity of Denys' tuberculin, beginning with 0·00001 c.c., and doubling this amount at each injection. The increase in dosage of this tuberculin is thus more rapid than in the case of the T.R.'s.

With females particular attention must be paid to the menstrual periods, and no inoculation should be performed within the space of time from three days prior to the onset of a period to three days after its cessation.

If treatment upon these lines be persisted in, uniformly successful results should be secured, assuming the diagnosis to have been correct. Prolonged treatment, however, may be necessary.

Choroidal nodules may be watched disappearing by means of the ophthalmoscope; gradually shrinkage occurring until nothing is seen but a white scar, or total absorption takes place. Interstitial keratitis should clear completely, and mutton-fat deposits disappear.

Conjunctivitis.

The forms of conjunctivitis to which vaccine therapy is especially applicable are:

1. Acute forms: Gonococcal, pneumococcal, streptococcal.

2. Chronic forms : Those due to the Morax-Axenfeld, the tubercle and Friedländer's bacillus.

In the acute forms, vaccine therapy is of especial service, in that extension to other parts can almost certainly be obviated if the case be seen early. In each of these infections a 250,000,000 dose of stock vaccine should be given as soon as the organism has been diagnosed from smears. Clinical signs are a quite sufficient guide to repetition, which may be performed in three or four days, best with a vaccine meanwhile prepared from the patient's own organisms. Such a case was one under Professor McHardy. It was seen by three members of the staff at the Royal Eye Hospital, and so bad a prognosis given that as a last resort I decided to give an immediate inoculation ; 250,000,000 of a stock gonococcal vaccine were given, and the index found to be 2·5. Although the patient was extremely negligent of himself, and could not be induced to use a lotion or guard to the other eye, improvement began immediately, and, despite the fact that on the fourth day the negative phase was still persisting, the index being only 1·26, marked change was evident. The active process was checked, there was much less chemosis and little discharge. Upon the eighth day the index was 3·8, and the condition of the eye so satisfactory that the patient could not be induced to make any further attendance.

Three cases of acute pneumococcal conjunctivitis, progressing to hypopyon ulcer, have also been subjected by the author to vaccine therapy within the past few months. Two of these cases were under the care of Dr. Willoughby Lyle, who has very kindly furnished the following notes upon them :

' A male, aged forty-nine, was suffering from a rapidly

infiltrating corneal ulcer, with hypopyon two-thirds up the aqueous chamber. Local treatment was persevered with for twelve days without any improvement whatever taking place ; in fact, the intra-ocular tension was raised and the local pain so great (and there was no perception of light) that it was almost decided to excise the eyeball. Vaccine therapy, however, was commenced, and local treatment persevered with. In four days the hypopyon began to disappear, and the cornea to clear at the margins. From that time until the patient left the hospital—four weeks later—the eye gradually improved. Altogether two injections of 250,000,000, and one of 500,000,000 pneumococci were given. On examination two days after leaving the hospital, the local condition was as follows : There was a large irregular leukomatous patch, somewhat vascular, over the lower two-thirds of the cornea, a narrow ring of clearer cornea below the leukoma. The margin of the pupil could just be seen over the nebulous cornea above. The intra-ocular tension was normal, and the patient could distinguish between light and darkness.

'The second case was in a child, aged three years seven months, who was admitted into the hospital with a central corneal ulcer with infiltrating margins and a small hypopyon. In spite of local treatment, the hypopyon increased, the ulcer spread, and the cornea ruptured. Vaccine treatment was commenced with a dose of 175,000,000 pneumococci, and from that time the eye began to clear. When the child left the hospital there was a large "leukoma adherens"; the cornea was somewhat vascular; there was a well-formed aqueous chamber; the iris was a good colour, and reacted readily to light.

'The favourable result obtained in these cases was

very largely due to the vaccine treatment, and but for it the first-mentioned patient would undoubtedly have lost his eye.'

The third case was under the care of Mr. L. V. Cargill, and was a very severe one. As soon as the pneumococcus was isolated, a dose of 250,000,000 of the pneumococcal vaccine which had been prepared for Case 1 of Dr. Lyle's was given. Improvement began within twenty-four hours, and progressed with extreme rapidity. The hypopyon was rapidly absorbed, and the patient discharged within a week.

Of the three forms of chronic conjunctivitis, two are, it is true, uncommon, but are singularly intractable to ordinary treatment. I refer to the forms due to the tubercle bacillus and the bacillus of Friedländer. The latter of these is especially intractable, and may persist for years; whereas improvement may be anticipated from the administration of a single dose of 250,000,000 organisms, and cure from three or four doses. The third form, by far the commonest variety of chronic conjunctivitis, is that due to the *Bacillus lacunatus* of Morax-Axenfeld, and occasionally proves very resistant to treatment, especially in old people. Such cases should receive two or three injections of 100,000,000 organisms at intervals of two or three weeks, clinical appearances being sufficient guide as to the appropriate time for repeating the injection. Should cure not result, one or two doses of 250,000,000 organisms will almost certainly achieve this end. This organism, though easy to isolate, yields but feeble growth, and the preparation of the vaccine is no easy matter. The results are, however, so satisfactory as to afford sufficient compensation for the trouble and expense incurred.

Corneal Ulcers.

The bacteriology of these is not well known. The tubercle bacillus and pneumococcus are certain causes of some chronic varieties. Acute ulceration may be due to streptococcus, staphylococcus, gonococcus, *Bacillus coli communis*, *Bacillus pyocyaneus*, and other organisms. No matter how high the index may be to an infecting organism in these cases, immediate injection of a stock vaccine should be made as soon as the infection has been identified. The preparation of a vaccine from the patient's own bacteria should then be proceeded with, and a fresh injection be given should no response to the stock vaccine be noticeable.

Of the chronic forms due to the pneumococcus, the ulcus serpens corneæ is the best known. Two such cases have been treated by the author, with complete success by means of autogenous vaccine. One of these deserves further mention. The patient was a man, eighty years of age, under the care of Mr. Brookbanks James, and was admitted with a very bad corneal ulcer. A large hypopyon was present; the cornea was very opaque, the iris bound down by adhesions, and the tension + 1·5. Cauterization, paracentesis, and, later, sclerotomy for the relief of tension and evacuation of the hypopyon, brought only temporary improvement, and excision seemed the only remedy. The condition was still acute when the pneumococcus was isolated and a vaccine prepared. Despite the high index to this organism—viz., 2·5—an injection of 250,000,000 organisms was given. Within three days the eye began to improve in appearance; at the end of a week the index was 4·2, and after a fortnight 3·0. A second injection was then

given, with the result that eighteen days later the index stood at 6·3, and the inflammation had quite subsided. A large partial staphyloma of the cornea which developed later was treated radically by excision without the use of sutures. No reaction followed the operation, and the final result was an eye in which some slight vision was preserved, and a firm flat scar in the cornea left in the site of the staphyloma. Several months later the eye was quite quiet and free from irritability.

The following case of ulcerative keratitis, under the care of Professor McHardy, at the Royal Eye Hospital, is not without interest : The patient had already had one eye removed for chronic ulcerative keratitis, going on to perforation, shrinking of the globe, and considerable pain. About eighteen months subsequently the second eye was also attacked ; general superficial erosion of the cornea went on to infiltration of the more superficial, then of the deeper layers of the cornea ; the tension fell considerably and vision was practically nil, only dim perception of light being possible. Cultures from the surface of the globe yielded large cocci not staining by Gram's method, which were apparently not the *Micrococcus catarrhalis*, and diplococci which morphologically resembled the pneumococcus, but could not be isolated. Upon the chance of the infection being a pneumococcal one, two injections of a vaccine were given without producing any good result ; on the contrary, the condition became rather worse. The vision was so bad that an iridectomy was decided on. The iris, when seized by the forceps, simply tore at once, it was so pulpy ; cultures were made from this small portion of iris and from scrapings of an eroded portion of the cornea, and the same non-Gram-staining coccus obtained from

both. The organism so far has not been identified, but a vaccine was made of it as a last hope. A first injection of 250,000,000 organisms, the index being 0·5, was followed, ten days later, when the index was 0·8, by a second of like amount; seventeen days after the first injection, the index being 1·5, the eye began definitely to improve, and steadily continued to do so. Twenty-eight days after the second injection the index was 2·6, and a further dose of 400,000,000 given. The eye was now very much better; vision was returning, fingers being seen at about 1 foot. In another twenty-six days the patient could discern faces fairly well, and a further injection of 500,000,000 cocci was given. A fortnight later vision was further improved, and the patient was discharged. When seen two months later, vision, both near and for distance = $\frac{1}{60}$; the cornea was diffusely nebulous; the eye was quite quiet, and vision had decidedly improved since the patient had left the hospital.

Mackay described before the Ophthalmological Society a case of phlyctenular keratitis. Tubercle bacilli could not be found, and the tuberculo-opsonic index was within normal limits. The staphylococcal index being 1·24, treatment with this vaccine was begun; improvement began immediately, but recurrences occurred when too long intervals were left between the inoculations.

The patient has remained well since completion of the treatment.

Brief reference may finally be made to the assistance afforded the surgeon in such conditions as recurrent 'hordeolum' and meibomians, for which staphylococci are responsible, and in chronic dacryocystitis, which, as Eyre has shown, is practically always due to the *Strepto-*

coccus pyogenes longus, whether subsequent to acute streptococcal conjunctivitis or to one of the other acute forms ; in this instance doses of 100,000,000 organisms may be begun with, and repeated or increased at intervals, best controlled by determinations of the index or, in default of these, by the clinical appearances.

APPENDIX

I. OPSONIC INDEX, DETERMINATION OF, TOWARDS SPECIAL ORGANISMS—PRACTICAL HINTS

1. WHATEVER the organism, use plenty of culture ; make a very thick emulsion ; centrifuge well ; pipette off upper layers ; dilute and centrifuge again ; dilute down upper layers to required density, which can only be judged by experience.

2. In tubercle determinations never use a dried-up culture or powder ; either preserve a growth, which has been proved to stain well, as a moist magma, killing by exposure to direct sunlight for twelve to twenty-four hours, or use a living culture and treat as above (1), making up the emulsion with 1·5 per cent. salt solution to avoid spontaneous phagocytosis.

3. The meningococcus and *Bacillus coli communis* are but slightly susceptible to phagocytosis when freshly isolated, especially by normal sera ; hence for diagnostic purposes it is well to employ a growth which has been repeatedly subcultured (ten to twenty times). In addition to these organisms, the *Bacillus typhosus*, *Micrococcus melitensis*, tubercle bacillus, and meningococcus are very apt to be agglutinated by ' immune ' sera. It is therefore well to employ a strain which has lost this property, bearing in mind, however, that the true opsonic power of the patient's serum to his own organisms has not thereby been determined.

4. In determining indices to the *Bacillus typhosus* and *Bacillus dysenteriæ*, Semple advises the following method: Dilute the serum 1 in 5; then heat it for fifteen minutes at 58° C., and take 2 volumes of heated and diluted serum, 2 volumes of washed blood-cells, and 1 volume of typhoid emulsion. Incubate for fifteen minutes at 37° C.; make films, and stain with Leishman's stain; then with 0·1 per cent. methylene blue for one minute to bring out the bacteria more clearly. By this procedure the bactericidal properties of the serum and the thermolabile opsonins are both done away with.

II. THE TUBERCLE BACILLUS.

A. Special Methods for its Detection from Various Sources.

1 *The Sputum.*—When the bacilli exist in but scanty numbers, either of the following methods will prove useful: Digest the sputum for twenty-four to forty-eight hours in the incubator with either pancreatic extract or with pepsin; centrifuge and examine the deposit. Or dilute the sputum with twenty times its volume of water, stir well, add a little dilute acetic acid to precipitate mucin and nucleo-albumin, filter, centrifuge thoroughly, and examine the deposit.

2. *The Fœces.*—Strassburger advises that a small particle be rubbed up with water, and centrifugalized for a very short time to throw down the large particles. The fluid, which holds the bacilli in suspension, is poured off and diluted with twice its volume of methylated spirit. This so reduces the specific gravity that the separation of the bacilli by the centrifuge is rendered quite easy.

Nabra's method is as follows: Place a small portion in a porcelain dish; dilute with alcohol at 40° C. until

complete disintegration has occurred; add a little ether, and stir thoroughly; allow to stand until the ether evaporates and a scum forms. This latter will contain all the microbial elements.

Rosenberger [1] examined the stools of 672 patients, in 60 of whom tuberculous infection had been diagnosed. Tubercle bacilli were found in 120, or 19·6 per cent., of the cases in which the diagnosis of tuberculosis had not been made, and in all the tuberculous cases. No acid-fast bacilli other than tubercle were found. In acute miliary tuberculosis they were always present, and in well-defined cases of pulmonary phthisis. Hence, the presence of tubercle bacilli in the fæces does not necessarily denote tuberculous enteritis. In all cases of chronic diarrhœa and of general glandular enlargement, search should be made in the fæces for the tubercle bacillus.

3. *The Urine.*—Dilution with two to three times its volume of methylated spirit will greatly assist the separation by centrifuge of the tubercle bacilli from urine.

B. Speedy Methods for the Isolation of the Tubercle Bacillus.

Two methods may be found useful. In the first a suitable lump of the sputum is washed well in sterile salt solution. Four parts of pure glycerine are then taken for every one part of sputum, and the mixture incubated at 37° C. for ten to fourteen days. Slight centrifugalization will throw down the tubercle bacilli, which may be pipetted off, washed with sterile salt solution, and used to inseminate tubes of broth and of nutrose glycerine agar. A pure culture is then usually obtained (Williamson).

In the second method animal inoculation is employed.

[1] *American Journal of Medical Science*, December, 1907.

A guinea-pig is taken, and its lumbar glands forcibly massaged. The inoculum is then introduced in the ordinary way, and the glands again massaged in a day or two. This has been found so greatly to increase their liability to infection that cultures may usually be obtained from them within a fortnight, instead of four to six weeks.

C. Special Staining Methods for the Tubercle Bacillus, with a View to the Differentiation of the Human and Bovine Varieties.

Spengler[1] has paid particular attention to this question. He lays especial stress on two points : (1) The necessity for making a thin homogeneous smear fairly representative of the whole secretion ; (2) the extreme importance of avoiding overheating, as this will destroy the envelope of the bacillus, which is composed of wax of a low melting-point. A thin film is made, and allowed to dry in the air. It is then dipped into 1 per cent. caustic soda solution and dried by most careful warming. The preparation is then covered with Löffler's methylene-blue, to give a ground colour to the envelope of the bovine bacillus (the envelope of the human variety is not thereby stained). It is then washed with water and stained with warm carbol-fuchsin, which is allowed to steam but slightly, and again washed with water. It is then counterstained for a few seconds with methylene-blue, to which one or two drops of 15 per cent. solution of nitric acid are added. This is then washed off with water, the slide dried between the filter-paper, and warmed very gently. 'If both human and bovine bacilli be present on

[1] *Deut. Med. Woch.*, 1907, No. 9.

the slide, little trouble will be found in differentiating them. The bovine has a so much thicker and sharper envelope than the human that it appears to be very much larger and thicker than the latter.'

In cases of tuberculosis which are approaching cure, or in whom the resistance is very good, the bacteria may fail to stain by ordinary methods, and Spengler advises the following procedure: Make a thin homogeneous smear as before; dry in the air, and stain with warm carbol-fuchsin, avoiding excessive heating. Without washing, add a mixture of equal parts of absolute alcohol and of either a saturated aqueous solution of picric acid or of Esbach's solution, leaving this in for two or three seconds. Then add three to four drops of 15 per cent. solution of nitric acid, and again picric acid alcohol for five to ten seconds, until the smear is of a light yellow colour. Wash with distilled water, dry carefully, wash with 60 per cent. alcohol; then for a few seconds with 15 per cent. nitric acid till a light yellow; again with 60 per cent. alcohol. Finally, contrast stain with picric acid alcohol until the smear is well coloured; wash with distilled water; dry and mount.

By means of these special methods, Spengler[1] has succeeded in demonstrating certain bodies which stain the same as the tubercle bacillus, and appear as though they might be cross-sections of bacilli. He now considers these bodies as true spores when of the bovine variety (being more resistant to heat than the bacilli), and as 'sporoids' when of the human type (being then less resistant). They sometimes appear as single bodies, but are often found in masses. These spore-forms especially occur when the culture medium is poor. They may be

[1] *Zeitschrift f. Hyg. u. Infect. Krank.*, Bd. xlix., 1905.

inoculated in good media and made to produce full-sized bacilli. They are found most plentifully in patients with good resisting power, because their tissues offer a poor culture medium. Spengler has often found these forms in the fæces in cases of intestinal tuberculosis, and in the blood in cases of acute miliary tuberculosis. To demonstrate these 'Splitter' forms, the first of the above methods is the better.

D. The Index to both Human and Bovine Types in Cases of Pulmonary Tuberculosis, and the Effect of Injections of the Two Varieties of T.R.

The index in pulmonary tuberculosis to the human and bovine types respectively, and the effect thereupon of injections of the two T.R.'s, has been investigated in a number of cases by Williamson, who has kindly supplied me with the following charts (Nos. XVII.-XXI.):

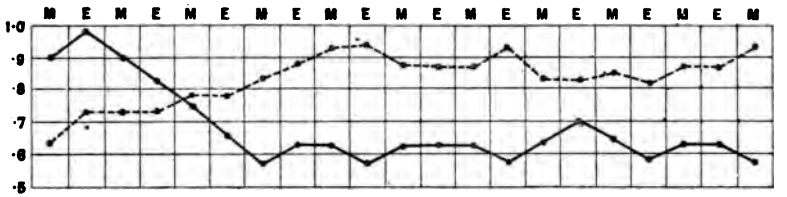
CHART XVII.

Index determined morning and evening, patient resting in bed. Dotted line = index to bovine type; continuous line = index to human type.

Chart No. XVII. is a typical one of six cases. The sputum contained abundant tubercle bacilli, and the patient rested in bed during the estimations. It will be seen that the indices to the human and bovine types respectively moved in inverse directions; when the index to the human type rose, that to the bovine fell, and *vice versa*.

Chart No. XVIII. exhibits similar features. Tubercle bacilli were numerous, and, according to Spengler's methods of staining, both types appeared to be present. It will be observed that, although the index to the bovine type rose from 0·6 to 0·94, that to the human fell from

CHART XVIII.

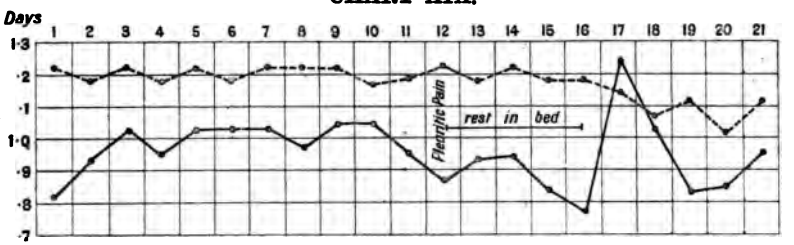


Index determined morning and evening, patient in bed; heavy lung exercises. Patient gained 13 lbs. in weight. Lines indicate as before.

1·0 to 0·6; despite this, the patient did very well, and gained 13 pounds in weight. The more important of the two infections would therefore appear to have been the bovine one.

That the indices to the two types do not always move in opposite directions is seen in Chart No. XIX. The

CHART XIX.



Daily determinations of index. Few tubercle bacilli in sputum. Temperature normal morning and evening upon graduated exercises. Upon the twelfth day developed a pleuritic pain, and was accordingly in bed till the sixteenth day. High index to the human strain upon the seventeenth day confirmed by a duplicate estimation.

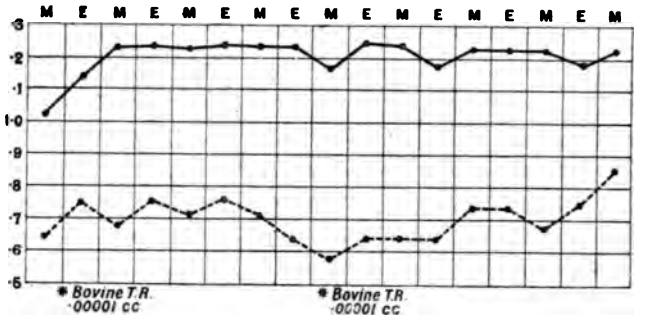
onset of a slight pleuritic attack raised the index to the human type from 0·8 to 1·2, without influencing that

to the bovine type to anything but a slight extent; the tendency is, however, there.

The effect of injection of a human T.R. upon the index to the human bacillus has been fully described in the text; the effect upon the index to the bovine bacillus requires further elucidation.

From Chart No. XX. it will be seen that an injection of 0·00001 c.c. of bovine T.R. had no effect upon the index

CHART XX.



Case of Very Advanced Phthisis, with Moderate Inverse Pyrexia.—Owing, perhaps, to advanced state of disease, immunizing response to injections poor. The indices point to bovine nature of infection.

to the human type in a case of advanced phthisis, whereas it produced a definite but slight rise in the index to the bovine type.

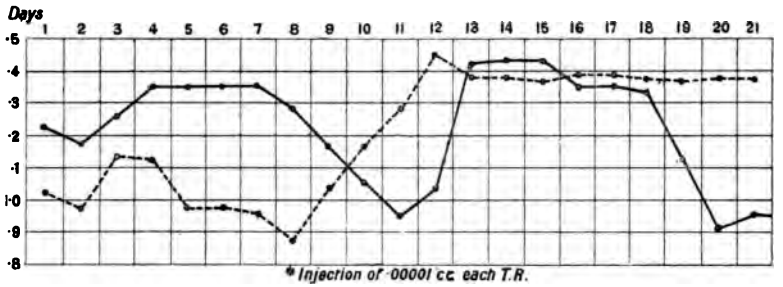
Chart No. XXI. shows very well the effects of injection of the mixed T.R.'s as advocated by the author during the past year. It will be seen that the indices to both types rose most satisfactorily. The dosage of the T.R.'s given was so small that no effect was produced upon the temperature; the moist sounds were, however, multiplied, and the character of the sputum altered.

These charts are only typical of many, and the work is to be continued; but, so far as it goes, it appears to

justify the author's contention that the human T.R. raises the index to the human bacillus, and only slightly affects that to the bovine bacillus, and *vice versa*; while an injection of the mixed T.R.'s causes elevation of the

CHART XXI.

To show Effect of Injection of Mixed T.R.'s upon the Indices to the Two Strains.



Case of Early Phthisis.—Upon the eighth day 0·00001 c.c. of each T.R. (human and bovine) were given. The effect upon the indices is seen in the chart. The temperature remained normal, the moist sounds were multiplied, and the sputum became slightly blood-stained.

index to both: so that, if opsonin be the important immunizing factor in tuberculosis, the mixed T.R.'s should be employed in all cases where the exact nature of the infecting organism has not been determined.

INDEX

PAGES

Acne - - - - - - - - - 150
„ dosage of staphylococcus vaccine - - - - 151
„ indurata - - - - - - - 151, 153
Actinomycosis : vaccine treatment - - - - - 212
Addison's disease : diagnosis by means of opsonic index - - 83
Adenitis : diagnosis of tubercular adenitis by opsonic index - - 83
„ dosage of tuberculin - - - - - 139
„ types of tubercle bacilli responsible for - - - 138
„ tubercular - - - - - - - 83, 137
„ use of mixed tuberculins - - - - - 116
Administration of vaccines - - - - - - 68
„ „ „ by the mouth - - - - 70
Anti-opsonins - - - - - - - - 14
Anti-typhoid immunization - - - - - 198, 202
„ vaccine - - - - - - - 199

Bacillus coryzæ segmentosus. See *Bacillus septus.*
Bacillus coli communis : emulsion - - - - 33, 227
„ „ „ group of bacilli - - - - 192
„ „ „ in genito-urinary disease - - - 147
„ „ „ in intestinal disease - - - - 147
„ „ „ in septicæmia - - - - 160
„ „ „ preparation of vaccine - - - 53
„ „ „ vaccine treatment - - - - 193
„ „ „ vaccine dosage - - - - 196
Bacillus of Friedländer - - - - 17, 18, 184, 222
„ „ „ preparation of vaccine - - - 54
„ „ „ vaccine in chronic nasal catarrh - - 190
„ „ „ vaccine in chronic gleet - - - 173
„ „ „ vaccine in acute nasal catarrh - 187, 189
Bacillus Morax-Axenfeld : conjunctivitis - - - - 222
„ „ „ emulsion - - - - - 33
Bacillus paralyticans - - - - - - - 207
Bacillus paratyphosus - - - - - - 192, 196
Bacillus septus - - - - - - 182, 185
„ „ differentiation - - - - - - 55
„ „ effect of vaccine on opsonic index - - - 18
„ „ preparation of vaccine - - - - 54

PAGES

Bacillus septus, use of stock vaccine - - - - 47, 186
,, ,, vaccine treatment of nasal catarrh - - - 188
Bacillus typhosus - - - - - - - 196
,, ,, determination of opsonic index - - - 227
Bazin's disease - - - - - - - 144
Blood : collection for estimation of opsonic index - - - 30
Blood-cells : preparation of, for opsonic index - - - - 31
Blood-films : method of spreading - - - - - 34
Boils - - - - - - - - - 153
Bovine tubercle : antagonism to human - - - 113, 232

Calmette's ophthalmo-reaction - - - - - 102, 215
Calcium salts : use of - - - - - - - 126
Carbuncles - - - - - - - - 153
Caries of superior maxillary bone - - - - - 143
Caseation in tuberculous adenitis - - - - - 139
Catarrh - - - - - - - - 184
,, bacteriology of nasal catarrh - - - - - 184
,, of accessory air sinuses - - - - - 185
,, tracheal - - - - - - 185, 189
,, treatment of acute catarrh of respiratory passages - - 186
,, treatment of chronic nasal catarrh - - - - 190
Catarrhalis, M. See *Micrococcus catarrhalis.*
Cholecystitis : vaccine treatment - - - - 193, 202
Chorea : Streptococcus rheumaticus - - - - - 164
Choroiditis - - - - - - - - 216
Clumps in opsonic slides - - - - - - 37
Colds : effect on opsonic index - - - - 17, 186
Colon bacillus. See *Bacillus coli communis.*
Combined vaccines : in acute catarrh - - - - 187
,, ,, in chronic gleet - - - - - 173
,, ,, in empyemata - - - - - 171
,, ,, in septicæmia - - - - - 161
,, ,, in tracheal catarrh - - - - 190
,, ,, preparation - - - - - 66
Conjunctivitis : chronic - - - - - - 222
,, gonococcal - - - - - 21, 46, 220
,, pneumococcal and streptococcal - - - 220
Corneal ulcer - - - - - - - - 223
Counting opsonic slides - - - - - - 37, 41
Cumulative phases - - - - - - - 24
Cystitis - - - - - - - - - 84

Dacryocystitis : chronic - - - - - - 225
Denys' tuberculin - - - - - - 117, 124, 130
Diagnosis by Calmette's reaction - - - - - 102
,, by means of the opsonic index - - - - 104
,, by means of the opsonic index during menstruation - 87
,, by opsonic index of gonococcal infection - - - 172
,, by opsonic index with diluted sera - - - - 88

PAGES

Diagnosis by the old tuberculin test - - - - - 99
„ by Von Pirquet's reaction - - - - - 102
„ of tuberculous infection - - - - - 99
Diluted sera in estimation of opsonic index - - - - 42
Diplococcus intracellularis (Weichselbaum). See Meningococcus.
Dosage of anti-typhoid vaccine - - - - - 199
„ of *Bacillus coli communis* vaccine - - - - 196
„ of meningococcus vaccine - - - - - 212
„ in corneal ulcers - - - - - 223, 225, 226
„ of Denys' tuberculin - - - - - 124, 130
„ in eye diseases - - - - - 219, 222
„ of Forster's vaccine in dysentery - - - - 204
„ of gonococcal vaccine - - - - - 177, 182
„ in gonorrhœal arthritis - - - - - 178
„ in gonorrhœal vulvo-vaginitis - - - - - 180
„ of pneumococcal vaccine - - - - - 168
„ in Malta fever - - - - - - 206
„ of Spengler's P.T.O. - - - - - - 124
„ of staphylococcal vaccine in acne - - - - 151
„ of staphylococcal vaccine in septicæmia and pyæmia - - 156
„ of streptococcal vaccine in septicæmia - - - 162
„ of tuberculin: theory - - - - - 21, 23, 25
„ of tuberculin: initial dose - - - - - 127
„ of tuberculin: T.A. (old tuberculin Koch) - - - 122
„ of tuberculin: T.R. and P.T.R. - - - - 125
„ of tuberculin: B.E. (human) and P.B.E. (bovine) - - 126
„ of mixed tuberculins - - - - - - 130
„ of tuberculin with guidance of opsonic index - - - 129
„ of tuberculin in tuberculous adenitis - - - - 139
„ of tuberculin (Turton's) - - - - - 135
„ in tracheal catarrh - - - - - - 190
Dysentery - - - - - - - - 202
„ treatment with vaccines - - - - - 204

Empyema: treatment with streptococcal vaccine - - - 162
Emulsion: preparation for opsonic index - - - 33, 227
„ preparation for vaccines - - - - - 58
Endocarditis: diagnosis by means of opsonic index - - - 83
Endometritis: diagnosis by means of opsonic index - - - 84
Enteric fever: treatment - - - - - - 201
Epididymorchitis: diagnosis by means of opsonic index - - 84
Episcleritis - - - - - - - - 219
Erysipelas: streptococcal - - - - - - 162
Exercise: effect on opsonic index - - - - - 71
Eye: vaccine therapy in eye disease - - - - - 215
„ tuberculous. See Ocular tuberculosis.

Furunculosis - - - - - - - - 153

Genito-urinary tuberculosis - - - - - - 145
Gonococcus - - - - - - - - 173

PAGES

Gonococcus emulsion - - - - - - - 33
,, medium for growth - - - - - - 47
,, method of obtaining culture - - - - 51
,, preparation of vaccine - - - - - 51
,, vaccine - - - - - - - 46, 177, 182
Gonorrhœa : acute - - - - - - - 178
,, chronic - - - - - 172, 173, 175, 176
,, chronic : treatment with lactic acid bacilli - - 177
,, dosage of vaccine - - - - 177, 182
,, importance of opsonic index in treatment - - 182
,, treatment - - - - - - 177
,, use of stock vaccines - - - - - 46
Gonorrhœal arthritis - - - - - - 178, 179
,, *conjunctivitis* - - - - - 46, 220
,, *vulvo-vaginitis* - - - - - - 180
Graduated exercise in treatment of tuberculosis - - - 128

Hæmophagocytic index : method - - - - - 43
Hordeolum - - - - - - - - 225
Human tuberculin, T.R. - - - - - - 138
Human type of tubercle - - - - - - 113

Infection with tubercle - - - - - - - 96
Inoculation of vaccines - - - - - - 68
Insane : opsonic index in the - - - - - - 80
Intestinal tuberculosis - - - - - - - 147
Irido-cyclitis - - - - - - - - 219
Iritis - - - - - - - - - 216

Joints : opsonic index in diagnosis of tuberculous joints - - 83
,, tuberculous - - - - - - 83, 139

Keratitis : opsonic index in diagnosis of tuberculous keratitis - 84, 216
Kidney : opsonic index in diagnosis of tuberculous kidney - - 83

Lactic acid bacilli injections in urethritis - - - - 177
Laryngitis : opsonic index in diagnosis of tuberculous laryngitis - 83
Lupus - - - - - - - - - 142
,, mixed infection - - - - - - 144
,, opsonic index in diagnosis - - - - - 84

Malta fever - - - - - - - - 206
Media for growths for estimation of opsonic index - - - 33
,, for growths for vaccines - - - - - 47
Meibomians - - - - - - - - 225
Meningitis : diagnosis by opsonic index - - - - 84
,, vaccine treatment - - - - - 210
Meningococcus : differentiation - - - - - 58
,, emulsion for opsonic index - - - - 227
,, preparation of vaccine - - - - 57

PAGES

Micrococcus catarrhalis - - - - - - 184
,, ,, differentiation - - - 56, 58
,, ,, effect of vaccine on opsonic index - - 19
,, ,, emulsion for opsonic index - - - 33
,, ,, preparation of vaccine - - - 56
,, ,, vaccine in nasal catarrh - - - 186
,, ,, vaccine in tracheal catarrh - - - 190
Micrococcus melitensis - - - - - 206
,, ,, emulsion for opsonic index - - - 227
Micrococcus neoformans - - - - - - 209
Mixed infection in tuberculosis - - - - - 133
Morax-Axenfeld bacillus : emulsion for opsonic index - - - 33
,, ,, ,, preparation of vaccine - - - 57

Nasal catarrh - - - - - - - - 184
Negative phase - - - - - - - 20, 86
,, ,, with tuberculin in tuberculosis - - 118, 121

Ocular tuberculosis - - - - - - - 149
,, ,, diagnosis - - - - - - 215
,, ,, treatment - - - - - - 218
,, ,, use of mixed tuberculins - - - - 116
Ophthalmo-reaction (Calmette) - - - - 102, 215
Opsonic index : accuracy of method - - - - - 39
,, ,, as a guide to diagnosis - - - - 81
,, ,, as a guide to immunization - - - 92, 126
,, ,, as an aid to prognosis - - - - 89
,, ,, effect of exercise in tuberculosis - - - 75
,, ,, effect of menstruation - - - 81, 87
,, ,, effect upon by T.R.'s of each type - - - 232
,, ,, hæmophagocytic index - - - - 43
,, ,, in acute and chronic diseases - - - - 80
,, ,, in cured sanatorium cases - - - 82, 136
,, ,, in disease - - - - - - 74
,, ,, in eye diseases - - - - 214, 216, 218
,, ,, in gonococcal infections - - - 172, 178, 182
,, ,, in health - - - - - - 71
,, ,, in infancy - - - - - - 73
,, ,, in pneumonia - - - - 168, 169
,, ,, in scarlet fever - - - - - 165
,, ,, in the insane - - - - - - 80
,, ,, in vaccine treatment of catarrh - - - 188
,, ,, in vaccine treatment of cerebro-spinal meningitis - 211
,, ,, method of determination - - - 29, 227
,, ,, methods of raising - - - - - 26
,, ,, method of determination - - - 29, 227
,, ,, relationship of infection to - - - - 17
,, ,, special methods in diagnosis - - - 85, 104
,, ,, to *Bacillus typhosus* and *Bacillus dysenteriæ* - - 228
,, ,, to *Streptococcus rheumaticus* - - - - 164

PAGES

Opsonic index: value in acute febrile conditions - - - 94
„ „ value in localized infections - - - - 93
„ „ value in treatment of tuberculosis - - 118, 127
Opsonins: demonstration of presence - - - - 5
„ fate in the organism - - - - - 16
„ nature and constitution - - - - - 6
„ site of formation - - - - - - 15
Osteo-myelitis - - - - - - - - 154
„ „ use of stock vaccine in - - - - - 46
Ovary: opsonic index in diagnosis of tuberculous ovary - - 84

Percentage index (Simon) - - - - - - 42
Periostitis - - - - - - - - 154
Peritonitis: diagnosis of tuberculous peritonitis by opsonic index - 83
„ tuberculous - - - - - - 147
Phagocytic index - - - - - - - 43
„ „ in anti-typhoid immunization - - - 200
Phlyctenular keratitis - - - - - - - 225
Phlyctenules - - - - - - - - 216
Phthisis. See Pulmonary tuberculosis.
Pleurisy: diagnosis of tuberculous pleurisy by opsonic index - - 83
Pneumococcus - - - - - - - 167
„ in metritis and pyosalpinx - - - - 171
„ medium for growth - - - - - 47
„ preparation of vaccine - - - - - 52
„ use of stock vaccine - - - - - 47
„ vaccine in corneal ulcer - - - - 223
„ vaccine in peritonitis - - - - - 171
„ vaccine in pneumonia - - - - - 167
Pneumonia - - - - - - - - 167
Positive phase - - - - - 20, 86
„ „ in tuberculin therapy - - - - - 121
Positive phase plateau - - - - - - - 20
Prognosis: opsonic index as an aid to - - - - 89
Puerperal fever: streptococcal - - - - - 157
Pulmonary tuberculosis: duration of negative phase - - - 22
„ „ effect of exercise on opsonic index - - 75
„ „ mixed infection in - - - - 133
„ „ opsonic index as an aid to prognosis - - 89
„ „ results of vaccine therapy guided by clinical symptoms - - - - 131
„ „ results of vaccine therapy guided by opsonic methods - - - - - 133
„ „ use of bovine T.R. - - - - 127
„ „ use of mixed tuberculins - - 116, 127
„ „ vaccine treatment - - - - 118
Pyæmia: staphylococcal - - - - - - 155
„ streptococcal - - - - - - 159

Rheumatism: Streptococcus rheumaticus - - - - 164

PAGES

Salpingitis : opsonic index in diagnosis of tuberculous - - 84
Scarlet fever - - - - - - - - 165
Septicæmia : staphylococcal - - - - - - 155
,, streptococcal - - - - - 159, 160, 161
,, streptococcal, dosage in - - - - - 162
Septus. See *Bacillus septus.*
Simon's percentage index - - - - - - 42
Sinus - - - - - - - - - 28
,, in tuberculous adenitis - - - - - 139
Spengler's method of therapy in tuberculosis - - - - 114
,, P.T.O. - - - - - - - 124
'Splitter' - - - - - - - - 112
Staining : blood-films for opsonic count - - - - 37
Standardization of vaccines - - - - - - 59
Staphylococcus albus vaccine - - - - - 49
,, *aureus* in septicæmia - - - - - 155
,, *aureus* vaccine - - - - - - 49
,, emulsion - - - - - - 33
,, vaccine in acne - - - - - 151
,, vaccine in furunculosis - - - - 153
Sterilization of vaccines - - - - - - 62
Stock vaccines : advisability of using - - - - - 45
Streptococcus - - - - - - - - 158
,, classification - - - - - - 157
,, emulsion - - - - - - 33
,, in dacryocystitis - - - - - 225
,, in scarlet fever - - - - - 165
,, in septicæmia - - - - - 159
,, preparation of vaccine - - - - - 49
,, *rheumaticus* - - - - - - 164
Streptothrix : vaccine treatment - - - - - 212
Sycosis - - - - - - - - 154
Synovitis of knee - - - - - - - 140

Tabes - - - - - - - - - 207
Technique of opsonic index - - - - - 29, 227
Temperature : as a guide in tuberculin therapy - - 121, 135
Toxæmia in tuberculosis - - - - - - 117
Toxin : toxins and antitoxins in human and bovine tubercle - - 115
Tracheal catarrh - - - - - - 185, 190
Tubercle bacillus : differentiation of human and bovine types - 107, 108
,, ,, emulsion - - - - - 34, 227
,, ,, human and bovine types - - 96, 105, 110, 230
,, ,, medium for growth - - - - 47
,, ,, methods for isolation - - - 48, 229
,, ,, special methods for detection - - - 226
,, ,, special staining methods - - - 230
,, ,, splitter - - - - - - 231
Tuberculin - - - - - - - - 117

PAGES

Tuberculin bacilliary emulsion - - - - - 117
,, B.E. - - - - - - - 125
,, Calmette's ophthalmo-reaction - - - 102, 215
,, choice of - - - - - - - 113
,, Denys' - - - - - - 117, 123, 130
,, dosage - - - - - 23, 25, 118, 122, 127
,, dosage without guidance of opsonic index - - - 128
,, in bones and joints - - - - - 139
,, in cured sanatorium cases - - - - - 136
,, in genito-urinary tuberculosis - - - - 145
,, in eye diseases - - - - - - 218
,, in tuberculous adenitis - - - - - 138
,, intervals in administration - - - 128, 130
,, method of making special - - - - - 47
,, negative phase with - - - - - 118
,, new T.R. (Koch) - - - - - 63, 117
,, P.B.E. - - - - - - - 125
,, preparation of - - - - - - 63
,, P.T.O. - - - - - - - 124
,, P.T.R. - - - - - - - 125
,, purified old tuberculin - - - - - 117
,, results in phthisis with opsonic index - - - 131
,, results in phthisis without opsonic index - - - 133
,, Spengler's P.T.O. - - - - - - 124
,, special : difficulty of making - - - - 45
,, T.A. old tuberculin - - - - 117, 122
,, T.O. (human) - - - - - 63, 124
,, T.R. - - - - - - - 125
,, use in diagnosis - - - - - 86, 99, 104
,, use of mixed human and bovine - - - 116, 130, 218
,, Von Pirquet's cutaneous reaction - - - - 102
Tuberculosis : ætiology - - - - - - 96
,, eye - - - - - - 116, 149, 215
,, genito-urinary - - - - - - 145
,, graduated exercise in treatment of - - - 128
,, intestinal - - - - - - 147
,, localized - - - - - 137, 142
,, methods of diagnosis - - - - - 99
,, of lungs. See Pulmonary tuberculosis.
,, opsonic index as an aid to prognosis - - - 90
,, opsonic index in - - - - - 74
,, secondary infections - - - - - 128
,, treatment under guidance of clinical symptoms - 122
,, treatment with vaccines - - - 120, 129
,, types—human and bovine - - - - 111
Tuberculous meningitis - - - - - - 148
,, *peritonitis* - - - - - - 147
Tubing vaccines - - - - - - - 62
Typhoid carriers - - - - - - - 201
,, group of bacilli - - - - - - 196

PAGES

Typhoid, immunization against - - - - - 198
,, specific therapy in - - - - - - 202
,, types of - - - - - - 196, 197

Ulcers : tuberculous - - - - - - - 144
,, corneal - - - - - - - 223
Urethritis - - - - - - - 172, 173, 175
,, differential diagnosis by opsonic index - - 84, 175, 176
,, treatment with *Bacillus coli communis* vaccine - - 195
,, treatment with lactic acid bacilli - - - - 177

Vaccine administration - - - - - - 68
,, by the mouth - - - - - - 70
,, effect on opsonic index - - - - - 18
,, gonococcus stock - - - - - - 46
,, preparation of - - - - - 45
,, preparation of anti-typhoid vaccine - - - - 199
,, preparation of combined vaccines - - - - 66
,, stock : advisability of - - - - - 45
,, treatment of tuberculosis - - - - 120
Von Pirquet : cutaneous reaction - - - - 102

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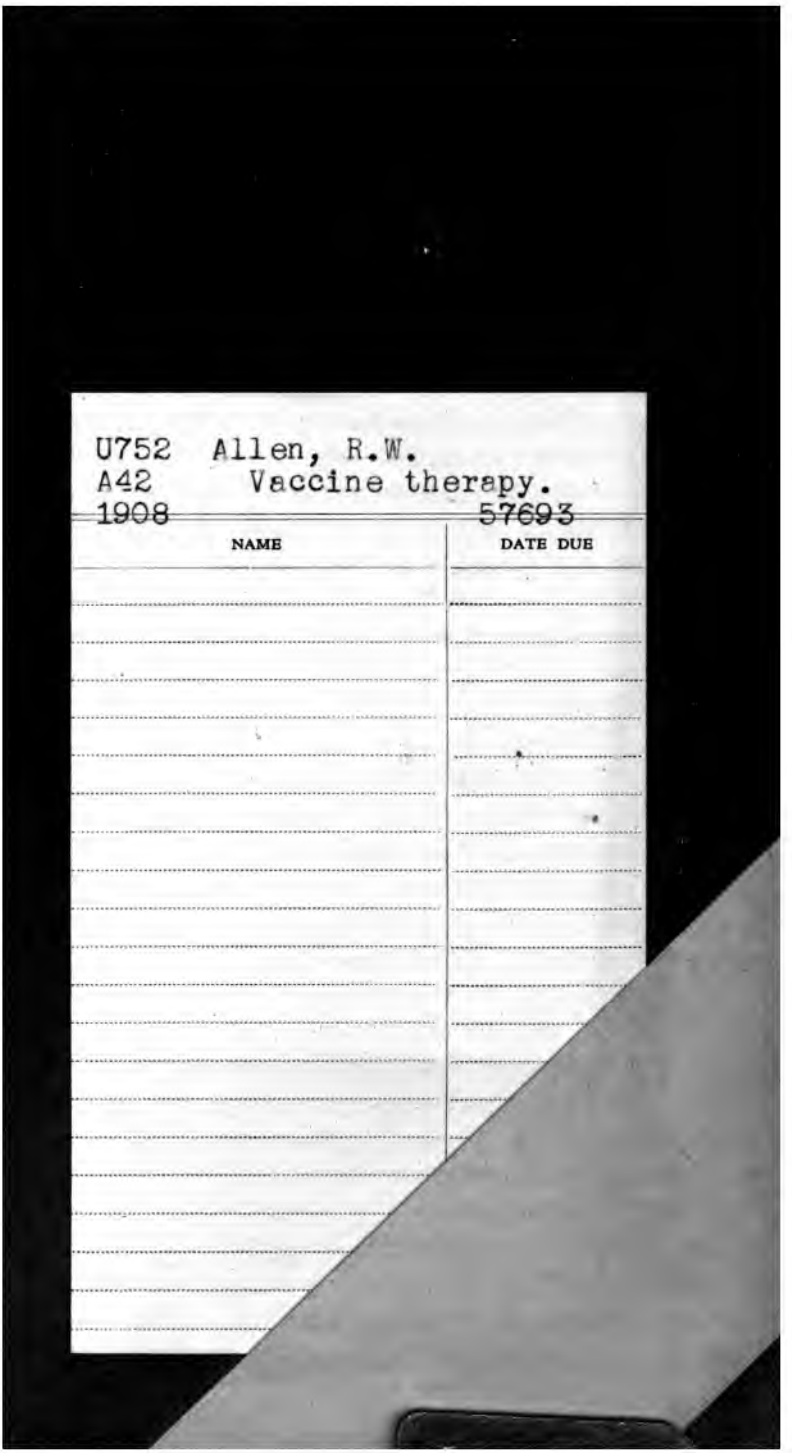
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